DEPRESSIVE STATES : A PHARMACOTHERAPEUTIC STUDY

DEPRESSIVE STATES :

A Pharmacotherapeutic Study

by

ANTHONY HORDERN M. B. Ch. B. (Univ. Edin)

M. R. C. P. Ed., M. R. C. P., D. P. M.

A thesis submitted for the degree of Doctor of Medicine at the University of Edinburgh.

CONTENTS

PREFACE

This thesis describes the methodology and findings of an investigation of the role of amitriptyline ("Elavil" "Tryptizol" "Tryptanol") in the treatment of female patients hospitalized with depressive states. At the conclusion of the investigation the rate of response that had been obtained was so high that a general review of the treatment of depressive states was undertaken for purposes of comparison. This review forms an introduction to the study.

In connection with the investigation the author acknowledges with pleasure and gratitude the contribution of three collaborators without whom it could not have been performed - Dr. C.G. Burt, Mr. N.F. Holt and Dr. W.F. Gordon. As Consultant Psychiatrist in charge of the female wards of Royal Park Psychiatric Hospital, Melbourne, Dr. Burt advised in planning, screened patients for inclusion, rated their progress with the author, classified and tabulated data and assisted in the clinical assessment of the findings. As Senior Research Psychologist to the Mental Health Research Institute, Melbourne, Mr. N.F. Holt performed the statistical computations necessary to evaluate the data and contributed to their interpretation. Dr. W.F. Gordon, Medical Officer at Royal Park Psychiatric Hospital, supervised the day to day care of the 137 patients included in the investigation, made a detailed assessment of side effects in the first 60 and helped with data collection generally.

In addition to the three principal collaborators, the author particularly wishes to thank Dr. J.F.J. Cade, Psychiatrist Superintendent of Royal Park Psychiatric Hospital, for his encouragement and support. Gratitude is expressed to the Nursing, Occupational Therapy, Out-Patient,

Social Service and Pathology Departments, and the Pharmacy of Royal Park Hospital; and to the Mental Hygiene Authority of Victoria. Miss June Donnell of the Adolph Basser Computing Laboratory at the University of Sydney kindly performed the factor analysis. In regard to the contents of the thesis the author wishes to thank Miss B. Wilson who drew the diagrams, Mr. R. Wilson who carried out the photography and Mrs. M. Dwyer who typed the manuscript. Finally thanks go to Merck Sharp and Dohme (Australia) Proprietary Limited, who provided the amitriptyline used in the trial and met the costs of the factor analysis; and also to Geigy (Australia) Proprietary Limited, who supplied most of the imipramine.

Melbourne
November 1962.

C H A P T E R I.

DEPRESSIVE STATES TODAY

In considering the role of a new compound in the treatment of depressive states, it seems mandatory to examine (1) the epidemiology of depression - to assess how significant a problem this illness constitutes today (11) the results of physical treatment, especially electroconvulsive therapy - to discern the advantages and drawbacks of these procedures and (111) the results of treatment with other drugs - for purposes of comparison in respect of therapeutic efficacy. This chapter, as an introduction to a study of efficacy of amitriptyline in depressive states, deals consecutively with these three aspects of depressive illness.

THE EPIDEMIOLOGY OF DEPRESSION.

"Depression" is an ambiguous term which, as Lehmann (1959) has pointed out, can connote a symptom, a syndrome or a nosological entity. "Depressive state" in the present context is more specific. It is used to denote the syndrome of a continuing state of pathological depression - ranging in depth from the profound gloom of a manic-depressive psychosis to the relatively trivial severity of a neurotic depressive reaction.

Mayer Gross, Slater and Roth (1960) remark that some three or four per thousand people suffer from affective disorders demanding psychiatric treatment. They point out that, although diagnostic criteria vary, true regional and racial differences exist in regard to these illnesses: thus, affective disorders are rarer in Northern Germany, Norway and Finland than in Southern Germany and Britain. Similarly, the 16.4 per cent of patients with affective psychoses admitted to mental hospitals

in Victoria, Australia, in 1951, is a higher figure than the 10.1 per cent admitted to similar institutions in the United States in 1950, though lower than the 32.1 per cent of admissions to mental hospitals in England and Wales in 1953-1962 (Krupinski and Stoller 1962). In Scandinavian countries, excellent parish records and geographically discrete, relatively homogeneous populations provide especially favourable conditions for ascertaining the incidence and prevalence of depressive states. Thus Odegaard (1946) found a disease expectancy in regard to manic depressive psychoses of 0.7 per cent in Norway; Larsson and Sjogren (1954) arrived at a figure of .9 per cent for men and 1.2 per cent for women in Sweden, rates corresponding to Stendstedt's (1952) overall morbidity risk of 1 per cent; and Fremming (1947) found a higher incidence still in Denmark - 1.64 per cent, 1.03 per cent for men and 2.24 per cent for women. According to Helgason (1960) the expectancy of developing manic depressive psychoses in Iceland is 2.09 per cent for both sexes combined, but is 1.32 per cent for endogenous depressions. It should be born in mind, however, that most authors exclude depressive neuroses, and since the cyclothymic temperament is frequently classified under neurosis, psychopathy or some physical diagnosis, the true incidence is probably higher - as much as 4-8 per cent according to Roth (1959). Supporting this higher estimate of risk, Sorensen and Stromgren (1960), who made an intensive study of the population of the island of Samso (some 7,000 individuals), found that 3.9 per cent of the population over the age of 20 years were suffering from depressive disease; the prevalence was much higher in females than males, and neuroses constituted 77 per cent of the cases. In Scania, Essen-Moller and Hagnell (1960) found that the cumulated life-risk of developing a depression increased up to 18 per cent for females and 9 per cent for males; the risk for psychotic depression alone was 1 per cent for both sexes taken together.

Apart from mental hospital admission figures, and epidemiological studies, another index of the prevalence of affective psychoses is provided by some developments in psychiatry in Great Britain. In recent years there has been a trend towards the development of psychiatric treatment in the wards of English general hospitals or in psychiatric units attached to such hospitals (National Association for Mental Health, 1961). The manageability and rapid response to treatment of most depressives, together with the advent of neuroleptics, has accelerated this tendency; thus Brooke and Stafford Clarke (1961) treated 325 psychiatrically ill patients in the wards of a general hospital in London: nearly three-quarters were suffering from an affective disorder and ECT was used in 102 cases. Capoore and Nixon (1961) now admit approximately 600 patients annually to a 56 bed unit in a general hospital of which some 53 per cent suffer from affective psychoses.

Many depressive states, however, as earlier pointed out, are inconspicuous or masked. Accordingly, to gain a clearer perspective of the problem, it may be helpful to consider the condition (1) as seen by the general practitioner; (2) as seen by the psychiatrist; (3) as reflected in the phenomenon of suicide; (4) as encountered in general hospitals and (5) as emerging, disguised, in alcoholism and amphetamine addiction.

DEPRESSION AS SEEN BY THE GENERAL PRACTITIONER

Apart from the treatment of infections and acute emergencies, much of general practice consists of the management of chronic illness, especially in elderly persons. In long-continued, painful diseases such as the arthritides, depression is a common concomitant; some degree of depression is commonly present in association with malignancies, and also

in such organic diseases of the central nervous system as cerebral arteriosclerosis and parkinsonism (Roth 1960a). Loneliness and poverty are additional burdens compounding depression that many patients, especially the elderly, have to bear. Where it is clear that depression is secondary, the general practitioner must direct his efforts to eradicating or ameliorating the cause through specific treatment; more general socio-psychological measures and even symptomatic antidepressant therapy may sometimes however be required.

In the ordinary course of practice, depressive states are often missed by general practitioners for a variety of reasons. In the first place, their undergraduate education has frequently lacked an adequate psychiatric teaching component (Hordern 1962). Secondly, some depressives present gay or smiling exteriors, attempting to minimise their symptoms, so that a subtle change in behaviour - an insidious loss of interest and vivacity, for example - may be the only clue to the true diagnosis. Again, as Ayd (1961a) and others have pointed out, some depressives complain of one or other symptom - insomnia, gastro-intestinal discomfort, headaches or fatigue - which leads the practitioner to make an erroneous diagnosis of physical illness; others are hypochondriacal and are mistakenly labelled neurotic, their underlying depressive state, which is of much more serious import, being missed. Some depressives go fruitlessly from physician to physician; over two decades ago Ziegler (1939) collected 111 patients who had first attended a physician or a surgeon because of depressive symptoms. Only recently has it been realized that the depressive colouring of the phobic anxiety-depersonalization syndrome, a not uncommon condition according to Roth (1960b), can also lead to diagnostic difficulty.

Despite these diagnostic problems, a number of valuable surveys of depression have been carried out by general practitioners. Two may be singled out for brief consideration. Watts (1956), who saw 529 depressives in a 10-year period in an English semi-rural practice of 8,000 patients, concluded that 36 per cent of all new psychiatric cases were depressives and that two-thirds of these patients were suffering from the endogenous category of this illness. Fifty-nine per cent of his cases were mild and could be managed personally, but 24 per cent required electroconvulsive therapy and the illnesses of 17 per cent were so severe they had to be admitted to hospital. The condition was commoner in women than in men, with a peak for both sexes between the ages of 45 and 50; not more than a quarter were seen by a psychiatrist. Though the majority recovered, Watts discovered that 14 per cent of his depressed patients ended in a chronic state, died in depression or committed suicide. The prognosis was worst in severe depressives, and was also poor among the aged, especially among men. Ryle (1961) investigated depressive illness in general practice in the course of a survey of the incidence of psychoses. Between 1956 and 1960 he studied 2,000 patients born before 1950 and calculated a disease expectancy rate for endogenous depression of 6.6 per cent for women and 1.5 per cent for men. Ryle concluded that his figures probably represented an under-estimate: whilst lower than those of Watts who had employed less stringent diagnostic criteria, they were higher than rates reported in mental hospital studies. In comparison with the figures computed by Norris (1959), for first admissions to three psychiatric hospitals in London, the inception rates in Ryle's practice were four times greater for men and eight times greater for women.

DEPRESSION AS SEEN BY THE PSYCHIATRIST.

Another approach to the problem of the epidemiology of depression is to examine the views of psychiatrists whose practice does not exclusively centre on mental hospital work. Mayer Gross (1954) and Partridge (1954) have emphasized the commonness of the disorder; Leigh (1955) analysing 1,000 domiciliary consultations, found that 34 per cent of them were for depressive reactions. Twenty-three per cent of the 8 per cent of specialist referrals made by Hopkins in 1956 were patients with depressive states. Within the last few years Roth (1959, 1960a) and Ayd (1961a), amongst many others, have emphasized the frequency with which depressive reactions occur and are seen by the psychiatrist. The recent resurgence of interest in the epidemiology of depression is presumably related to the advent of antidepressant compounds which currently provide an acceptable, widely applicable form of therapy for this condition.

SUICIDE.

The most dangerous complication of depressive illness is suicide, though suicide, especially in young adults, is not always associated with depression. The risk of suicide, pari passu with the incidence of endogenous depression, increases with age. Thus, in children under 12, suicidal attempts are rare; they are four to six times as common in adolescence, and become commoner still in adult life. Below the age of 30, nine times as many females make attempts as males, but over 30 the ratio reverses: three times as many men as women attempt suicide. Remarking that the young seldom communicate their suicidal intentions, whilst older individuals frequently do, Ayd (1962) puts forward the accepted view that, below the age of 30, it is usually the tense, deluded

schizophrenic who commits suicide, whilst, above that age, suicides suffer from the depressed phase of an affective psychosis (including involutional melancholia) or alcoholism. Before discussing suicide in adult life and old age, however, some general data on suicide will be scrutinized in order to underline the magnitude of the social problem it constitutes in almost every country today.

According to Hirsch (1959), in the United States between 16- and 20,000 people kill themselves each year - a rate of 11.2 per 100,000 population, making it the eleventh commonest North American cause of death. Even so, since many suicides are hushed up, the actual number of deaths from suicide is probably nearer 50 - 60,000 per year. In England and Wales, some 5,000 people kill themselves each year (Capstick 1960), and, according to a recent Annotation (1962) in the British Medical Journal, the last decade has seen a notable increase in the number of suicides. In Scotland the total was 50 per cent higher in 1960 than in 1950, the increase affecting both sexes, males rather more than females. In 1957, Australia had 1,170 suicides, a rate of 12.1 per 100,000, putting it in the top quarter of 60 countries listed in the Demographic Tables of the United Nations. Dax (1961) has suggested dividing countries with a high suicide rate into two groups - those which have a high rate of alcoholism (Switzerland, Sweden, Finland, Denmark and France) and those in which a high rate is associated with cultural factors (Japan, Germany and Austria). The rate for Victoria, Australia, in 1956-58 at 8 per cent per 100,000 was, Dax remarks, substantially below the figure for Australia as a whole.

The incidence of attempted suicide is variously estimated as five to ten times the incidence of the successfully completed act. According to Stengel (1952), attempted suicides and suicides comprise two different but overlapping populations. A recent Leading Article (1961) in the British Medical Journal states that the number of suicidal attempts occurring annually in England and Wales may currently be as high as 40,000, though of these only a small proportion - perhaps about 1 per cent per year of follow-up - eventually commit suicide. Both suicide and attempted suicide is commoner in people who are socially isolated : the rate falls from a high point in cities over 100,000 to a low point in rural areas. According to Carstairs (1960), in Britain, in any one year, there are 12 suicides and 30 attempted suicides per 100,000 population, giving an average of one attempted suicide per year and one successful suicide every three years per general practice of 2,500. Watts (1960) lost 12 patients from suicide in 15 years in a practice of 8,000.

Research into suicide has mainly involved a retrospective correlation with social factors in the time-honoured pattern established by Durkheim (Stengel 1960a). Regarding modes and fashions of suicide, men habitually terminate their lives in more violent ways than do women; the method adopted is closely related to the availability of suitable agents. Analysing 32,000 suicides in the State of New York between 1925 and 1954, Hirsch (1960a) found the commonest methods were gassing (30%), hanging (20%), jumping from heights (16%), taking poison (13%), and using firearms (8%). Since 1943, the use of barbiturates for suicide has increased fourfold, and in 1954 they were fifteen or sixteen times as commonly used as other agents; they are now being displaced for this purpose by the tranquillisers. The dynamics of suicide, according to Hirsch (1960b)

centre round the constellation of loss (real or fantasied), aggression (the chief dynamic force producing the act) and depression (which is commonest later in life). Nevertheless suicidal attempts have very complex motivations and, as Stengel (1960b) observes, no ready formula exists to encompass them. One fact has become increasingly apparent in recent years - suicide in older people is usually a deliberate, carefully contemplated act and, in as many as 70 per cent of cases, a prior communication of intent to suicide is made to the family or to friends (Capstick 1960). The communication may be posthumous, by means of a suicide note, as described in an Annotation (1961) in the British Medical Journal, reviewing a number of studies of this aspect of suicidal communication.

According to Stengel (1960a) "no reliable criteria for the prediction of suicide have been established beyond the high incidence in depressive illness". Thus, a depressive illness is the condition most strikingly associated with successful suicide; and according to a Leading Article (1961) in the British Medical Journal, some 14 per cent of patients with psychotic depression end their lives in this way. Dorpat and Ripley (1960), studying 114 consecutive suicides in the Seattle area of the United States through interviews with relatives and friends, found that psychotic depression had preceded the suicide in 17.6 per cent of cases, and psychoneurotic depression in 12 per cent. Capstick (1960), who studied 881 suicides in five years in Wales, found that 39 per cent of suicides had been depressed prior to their demise; and Nomura (1960) found that 29.7 per cent of 1,457 suicides investigated in two Japanese institutions were suffering from endogenous depressions. Nevertheless, the relationship of depressive illness to suicide is somewhat obscure in that, although the risk of suicide is undoubted in severe cases, it is uncertain which patients will

attempt suicide and which will not. Walton (1958) carried out an interesting investigation of this problem by examing the case notes of 223 depressives admitted to the Maudsley Hospital, London in 1955, in regard to attempts and threats of suicide. Dividing his cases into those which appeared definitely suicidal (attempts with or without definite threats) and those which did not, Walton found that there was no correlation between suicidal behaviour and social isolation or social degeneration, but that such behaviour was highly significantly correlated with parental deprivation (loss of a parent before the age of 14, repeated parental strife or a feeling of prolonged estrangement). Age was not correlated with suicidal behaviour but women showed such behaviour considerably more often than men; no association was found between suicidal behaviour and type of depression, i.e., endogenous or reactive categories.

Suicidal attempts, in general, peak between the ages of 55 and 64, the highest incidence for women being between the ages of 45 and 54, and that for men occurring a decade later, continuing at four to five times the female level throughout the remainder of life (Roth and Morrissey 1952). Nevertheless, in recent years suicide rates in females have been rising and are still on the increase, especially in the elderly (Mayer Gross, Slater and Roth 1960). This increase, as Sainsbury (1960) has pointed out, is probably due to factors other than the economic hardships of old age, and there is general agreement that three groups of causes are broadly responsible: mental illness, physical disease and social problems. Regarding the former, Batchelor and Napier (1953), O'Neal, Robins and Schmidt (1956), Capstick (1960) and others agree that pathological depression precedes suicide in about half of all cases. Affective psychoses are common conditions which increase in frequency up to a certain

age in both sexes; and since the peak incidence of suicide is a decade higher in men than in women, it may very well be that the higher incidence of suicide in older men is due to the gene which is instrumental in causing the condition being pushed to the end of reproductive life by genetic modifiers (Roth and Morrissey 1952). In regard to the part played by physical disease, Sainsbury (1960) concurs with earlier investigators that it can contribute significantly to suicidal behaviour, both directly through restricting activities and indirectly in many other ways. Thus physical illness, by threatening earning capacity, may produce anxiety in a breadwinner by arousing in him fears for the economic future of his family; such illness may also be a factor in alcoholism, which is commoner amongst males, and is frequently associated with suicide. Finally, with regard to social factors, Sainsbury's (1961) findings show that antecedent loneliness and bereavement are significantly more common in elderly suicides than in younger individuals attempting (and achieving) a similar goal. The true significance of these factors, however, probably lies in their effect in precipitating rather than causing the depressive psychoses which at one time in the elderly, were so frequently missed (Roth and Morrissey 1952).

DEPRESSION IN GENERAL HOSPITALS.

As pointed out earlier, the symptoms of depressive illnesses can readily suggest physical disease, especially if a depressive affect is not prominent and the disorder be manifested solely in hypochondriacal complaints. Since, unless the depression remits or appropriate therapy is given, such symptoms persist, a not inconsiderable proportion of depressed patients present in general hospitals, where the true nature of their condition may or may not be recognized. In a five-month survey of

the consultations seen by staff of the Department of Psychological Medicine at an English teaching hospital, of 77 patients referred, 27 had melancholias and 16 were given ECT. There were also 21 patients with neuroses, of whom 7 had psychoneurotic (reactive) depressions (Hordern 1955). In Scandinavia, Helsberg (1958) examined 500 adult patients attending Aarhus County Hospital between December 1947 and December 1948. Only 288 had "pure" somatic illnesses and in 134 (22%), psychiatric disorder was present. Depression, suicidal attempts and manic-depressive psychoses together constituted 22 per cent of these cases, i.e., they made up some 4 per cent of all admissions, but the incidence of depression would have been higher had some neurotics been included.

A further study of psychiatric illness at a medical and a surgical out-patient clinic in London has recently appeared in print. Culpan and Davies (1960), as a preface to their investigation, summarize eleven previous studies which together include 6,842 patients; the mean incidence of "pure" psychiatric illness was 27.3 per cent. In their own investigation Culpan and Davies found that, of 100 consecutive newly referred medical outpatients, 51 had a psychiatric illness and in 38 no relevant organic disease was present; in 100 new surgical outpatients 21 had psychiatric illnesses, but in only 5 was no organic component present.

ALCOHOLISM AND AMPHETAMINE ADDICTION.

Many years ago alcoholism was regarded as a cause of mental illness in general, apart from those specific psychiatric disorders - delirium tremens, Korsakov's psychosis, alcoholic pseudoparanoia - which are directly related to its excessive use. Kraepelin (1921), however, though an abstainer himself, regarded alcoholism as a symptom rather than a cause

of mental illness, an opinion echoed by Henderson and Batchelor (1962). Dipsomania, in particular, is probably symptomatic of a manic depressive psychosis, and the alarming results that a combination of alcohol and a disturbed mood state can sometimes produce have been remarked by Mayer Gross, Slater and Roth (1960). Because of its end result, alcoholism has been described by Karl Menninger (1938) as "chronic suicide". Whether this is so or not, the incidence of actual suicide is very much higher in alcoholics than it is in the general population. Lemere (1953) found a rate of 11 per cent in 500 followed-up alcoholic patients; in a more recent study of 131 voluntary patients discharged from Maudsley Hospital after treatment for alcoholic addiction, which was analysed in combination with data from a second series of 87 patients admitted to a London Observation Ward, Kessel and Grossman (1961) found an incidence of suicide of 8 per cent and 7 per cent respectively. In regard to overt depression, of a series of 161 alcoholics treated in the Payne Whitney Clinic, New York, since 1932, 6.8 per cent were found to be suffering from depression in middle or later life (Sherfey 1955). The evidence, therefore, would seem to suggest that a definite, if subtle, relationship exists between alcoholism and depression, and that the latter condition may, on occasion, present as the former. Cade and Krupinski (1962) recently tested the hypothesis that alcoholism in the male might substitute for depression in the female. They examined the incidence of depression in alcoholic and non-alcoholic migrants to Victoria, Australia; however, in the Southern European (non-alcoholic) group, the magnitude of the differential sex incidence of depression was maintained, a finding tending to refute their hypothesis. Finally, aside from these and other published figures, the author's experience suggests that some people drink to alleviate a state of depression or despair. It would seem logical

therefore, to suppose that in a proportion of alcoholics, depressive conditions underlie their alcoholic behaviour. The difference between such an individual and the overt depressive is probably to be sought in the genetic inheritance and the personality of the patient.

A less common, but still prevalent, way in which depression may present is an addiction to amphetamines. Besides producing a schizophrenic-like psychosis (Connell 1958), excessive amphetamine consumption can aggravate pre-existing psychiatric abnormalities and lead to adverse social consequences. Kiloh and Brandon (1962) have drawn attention to the huge quantities of amphetamine currently being prescribed and have described the lengths to which addicts may go to obtain these drugs. Habituation, which occurs mainly in chronically neurotic women, is not uncommon; according to Kiloh and Brandon those who become habituated often lack confidence, suffer from neurasthenia or react to adverse social consequences with depression. Two of the six illustrative cases described by McCormick (1962) to portray the side effects of amphetamine addiction used the drug because of depressive episodes, and two others may also have become addicted for this reason. Thirteen of fourteen amphetamine addicts described by Bell and Trethowan (1961) experienced clear mental stimulation after taking the compound; in many cases a mood change approaching elation was produced together with increased confidence and libidinal stimulation; depression was the commonest symptom following withdrawal and tendencies to suicide were noted. In some amphetamine addicts, electroconvulsive therapy has been reported to reduce the craving (Kennedy and Fish 1958). All this suggests that a proportion of depressives may be found amongst amphetamine users and that the practice of taking this drug may be, in some individuals, a symptom of an underlying depression.

PHYSICAL TREATMENTS FOR DEPRESSIVE STATES

CONVULSIVE THERAPY

The successful treatment of the vast majority of severe depressive states depended, until the advent of antidepressant drugs, on the artificial induction of epileptic-like convulsions. Indeed, convulsive treatment originated in a supposed antagonism between schizophrenia and epilepsy; Meduna, who first reported the technique and results of pharmacological convulsive treatment in 1935, originally used intramuscular injections of camphor to produce fits. Clinical trials soon began on the Continent of Europe but were more slowly undertaken in English-speaking countries, partly, Kennedy (1940) observes, because of traditional caution and partly because, at the time, attention was focused on treatment with prolonged narcosis and insulin. Meanwhile, in 1934, the uncertainty and delay with which camphor produced convulsions led Meduna to substitute pentamethylene tetrazol ("Cardiazol" "Metrazol") which produced a more predictable response and could be given intravenously. Though many did not agree with Meduna's basic hypothesis, his treatment proved to be of definite, if limited, value in schizophrenia (Harris 1938). Nevertheless, it soon became evident that it was potentially of much greater value in the treatment of patients with affective psychoses. Thus Low, Sonenthal, Blaurock, Kaplan and Sherman (1938) reported recoveries in 13 out of 16 manic-depressives given Metrazol, and the results of pharmacological convulsant therapy in patients with depressive states remained constantly good, for it was both more effective and less dangerous than prolonged narcosis. Fitzgerald (1943), reviewing the results of pharmacological convulsant treatment in eight reports covering 377 depressed patients, arrived at an overall improvement rate of 84 per cent (59% recovered or

greatly improved and 25% improved), an order of betterment paralleled, but never convincingly surpassed, by electro-convulsive therapy.

Cerletti, the originator of electroconvulsive therapy, like Meduna, was also interested in epilepsy. Seeking originally to devise a method of inducing epilepsy in dogs, he bagan to study the problem of the maximum amount of electricity that could safely be given without producing death or disastrous sequelae. The result was the discovery that, given in suitable amounts, electric current, applied through cephalic electrodes, could rapidly and safely induce convulsions indistinguishable from epilepsy. He gave the first electric convulsive treatment to a 39 year-old male schizophrenic in Rome in 1938.

The efficacy of electroconvulsive treatment, combined with its convenience, cheapness, rapidity of application and safety, soon led to its adoption on an extensive scale. Since the treatment was not accompanied by the terrifying sensations that had attended the administration of pentamethylene tetrazol, patients preferred ECT to pharmacological shock therapy, as also did hospital staff. Thus, in 1942, Kolb and Vogel, reporting the answers to a questionnaire sent to 305 North American hospitals, stated that a third of these hospitals said that they used all three shock treatments - electrical, cardiazol and insulin - and that 60 per cent preferred ECT, whilst only 8 per cent showed a preference for pharmacological convulsant therapy. The latter treatment was gradually discarded as, in the course of time, a number of new techniques were developed which, whilst rendering ECT less disturbing to patients, cut down the incidence of fractures, dislocations and other unwelcome complications.

To begin with, sedatives, together with parenteral atropine,

were given prior to therapy which, though generally administered to in-patients, also came into outpatient use. Curare was the first of a number of muscle relaxants which, given intravenously, was found to modify the muscular component of the convulsions; however, by 1953, curare had been generally replaced by succinylcholine, a safer and more convenient drug (Wilcox and Wilcox 1954). These compounds did not diminish the central side effects of ECT - cumulative memory disturbance and confusion - but by obviating the Valsalva phenomenon (the sudden increase of blood flow into the heart at the end of the convulsion), they safeguarded the heart as well as the skeletal system. This was a most desirable development, for sudden cardiac failure was (and is) the commonest cause of the infrequent deaths that follow ECT (Tewfik and Wells 1957). In addition, thiopentone anaesthesia, with or without the inhalation of oxygen, was employed by many to induce sleep prior to treatment (Impastato and Berg 1956). Subsequently, a few therapists began to omit the anaesthetic, devising special techniques, such as the so-called P.M. - G.M. method, to lessen the pre-shock anxiety that relaxants given alone, as a result of paralysis of respiratory muscles, were prone to evoke (Impastato and Gabriel 1958).

A second approach to the problem was to alter the electric impulse through modification of the electroconvulsant apparatus. These developments have recently been reviewed by Goldman (1962). The use of glissando and other techniques, however, whilst leading in general to fewer skeletal complications, has not resulted, Mayer Gross, Slater and Roth (1960) observe, in any appreciable lessening of post convulsive confusion and disturbance of memory. Indeed, although the mode of action of ECT remains unknown - Ulett (1962) recently stated that the literature lists more than three score theories purporting to explain the action of ECT -

experience has shown that the results of modified and unmodified ECT are virtually identical (Seager 1959) and that the treatment, in general, is extremely safe. In 1959 Barker and Baker sent a questionnaire to 13 London teaching hospitals and 42 other hospitals; they found that thiopentone and succinylcholine were used at 60 per cent of institutions, while thiopentone alone was used in 84 per cent; in less than 50 per cent of hospitals was an anaesthetist present during treatment. The death rate was one in 28,000 treatments - a fatality rate of .0036 per cent. This figure is somewhat lower than that arrived at by Perrin (1961) who, summarizing eleven large series, arrived at an estimated rate of 1 death per 1,000 cases.

ECT, like pharmacological shock therapy, initially was widely used in schizophrenia but, like the earlier treatment, soon found its most fruitful application in affective psychoses, particularly of the depressive type. Thus Sargant and Slater (1944), discussing the status of ECT in the first edition of their well-known work on physical treatment, observed that in the treatment of involutional depression, successes of the order of 70-80 per cent had been reported; this was, they felt, a great step forward, for previously these states were very refractory to treatment. The two authors went on to state that the swings of mood of patients with affective psychoses were more resistant to ECT than involutional depressions, and that, in manic-depressive depressives under 40 years of age, ECT could produce a troublesome temporary mania, or perhaps only a transient alleviation of their symptomatology. The best results were obtained, Sargant and Slater thought, when the depressive phase had lasted an unduly long time. In certain reactive depressions also, there was, they believed, a place for electroconvulsive therapy.

Since ECT was, until comparatively recently, one of the very few treatments in psychiatry that was simple, effective and safe, a tendency understandably developed to administer it to patients whose illnesses did not exactly conform to the patterns in which the best responses were to be anticipated. This, together with the dissimilar diagnostic criteria employed by different investigators, probably explains the discrepant rates of response that have been reported in depressive states. For purposes of subsequent comparison, it is worth examining the views of some leading authorities as well as scrutinizing a number of investigations in greater detail.

In the United Kingdom, Henderson and Batchelor (1962), in the latest edition of Henderson and Gillespie's textbook, state that of all depressive illnesses, involutional melancholia responds best to ECT, an 80 per cent rate being usual. Although manic-depressive depressives also respond, they do so most effectively, the two authors believe, when the nadir of their depression is passed; given earlier, ECT can, Henderson and Batchelor believe, produce a temporary improvement followed by a rapid relapse. In less-typical recurrent depressions which run courses longer than average - cases characterized by hypochondriasis, and in younger people, by unreality and anxiety - ECT may make the picture worse. Further, it is of little value in neurotic depressions. Lewis, (1956), in his section on mental illness in the ninth edition of Price's Textbook of Medicine, states that women suffer from depression more than men, and that first attacks of melancholia in late middle life clear up in two-thirds of cases. He gives no percentage response rates to ECT, though he considers that it is effective in older patients, remarking that its value in younger cases is uncertain. Mayer Gross, Slater and Roth (1960) in the second edition of

their textbook, whilst strongly advocating the use of ECT in affective disorders, particularly in involutional depression, give no figures with which to assess its efficacy. It is difficult to find, in any of these three endorsements, data regarding the rate of relapse of ECT - treated patients after discharge.

The views of authorities in the United States are very similar. Appel, Myers and Scheflen (1953), summarizing 17 studies in which ECT had been given to 6,551 patients with affective psychoses, found an improvement rate of 71±10 per cent with ECT in contrast to a rate of 58±20 per cent in patients treated conservatively. Kalinowsky (1954), who once worked with Cerletti in Rome, stated that in his opinion between 80 and almost 100 per cent of depressives responded to ECT. He noted that opinions had been expressed that future episodes tended to occur sooner in cases treated with ECT rather than conservatively; but in view of the rapidity with which ECT brought relief, together with the way it cut down hospital stay, he regarded this as an academic question. Writing five years later in the American Handbook of Psychiatry, Kalinowsky (1959) stated that some statistics for ECT in typical psychotic depressions came close to 100 per cent recovery of episodes: such patients responded equally well whether their depressive states were manic-depressive, involutional or geriatric. Results were poorer in depressives with neurotic reactions characterized by listlessness, dejected mood and anhedonia; indeed in these cases iproniazid was sometimes superior. He again remarked the prevalent clinical impression that intervals between episodes were shorter after depression had been treated with ECT instead of having been allowed to recover spontaneously. Bigelow (1959), describing involutional psychoses in the American Handbook, states that 90 per cent of involutional melancholics respond to a course of about

fifteen electroconvulsive treatments. Alexander (1958), another American authority, gives the following figures in his monograph on objective approaches to psychiatric treatment; for involutional melancholics treated on a conservative regime and/or intensive psychotherapy, 44 per cent response in contrast to 82 per cent improvement in those treated with ECT: for manic depressive depressives, 53.7 per cent improvement when treated conservatively versus 67.9 per cent recovering after ECT. In the State of New York, Alexander remarks, 70 per cent of cases of affective psychoses treated with ECT had spent less than two months in hospital versus 18 per cent of conservatively-treated controls. According to this author, in 116 cases the rate of spontaneous recovery of depression (including both complete and social recoveries) was 66.4 per cent, materializing during the first year in only 44 per cent of cases; intensive psychotherapy, which achieved 46.4 per cent of recovery in 208 cases, could not better these figures. On the other hand, in depressives treated with ECT the rate of complete or social recovery in 2165 cases was 67.9 per cent.

TABLE 1.

RESULTS OF ELECTROCONVULSIVE THERAPY IN 2028 DEPRESSED PATIENTS

NO. & SEX of PATIENTS	DIAGNOSIS	AV. NO. of E. C. Ts.	PERCENTAGE SUCCESS	AV. DURATION of HOSPITALIZATION	RELAPSE RATE	FOLLOW-UP PERIOD	REMARKS	SOURCE
92 F. 58 M.	Psychotic depressives	17	82%	Approx. 3 months	8%	1 year	Follow-up incomplete	Fitzgerald 1943.
100 F.	Depressive psychoses	6 - 9	87%	Approx. 1 month after last E. C. T.	13%	? 6 months	Follow-up period uncertain	Batt 1943.
300 F.	Melancholia	10 +	80%	Approx 3 months.	13.5%	3½ years		Kino & Thorpe 1946.
42 F. 19 M.	Involutional psychoses	8	80%	6 weeks median	31%	3 years		Huston & Locher 1948a.
49 F. 25 M.	Manic depressive psychoses	7	88%	9 months median	17%	3 years		Huston & Locher 1948b.
40 F. 21 M.	Involutional psychoses	11-16	88%	6 months	?	?		Fishburn 1949.
608 F. 315 M.	Depressive states	7 7	82% 88%	See text	18.9%) 21.4%)	1 year	15.3%) 21.4%) at 6 months	Karagulla 1950.
219 F. 88 M.	Depressive states	5-6	97%	5 - 7 weeks	23%	13 months	26% at 1 month	Thomas 1954.
52 ?	Endogenous depressives	?	94%	3 weeks +	48%	6 months	See text	Kiloh, Child & Latner 1960.

Table 1 summarizes the salient findings in nine investigations of the immediate response to and relapse rate after electroconvulsive treatment was given to 2028 patients with depressive disorders. With the exception of Karagulla (1950), all the other investigators cited in the table agree that, given in depressive disorders, ECT alleviates suffering, increases the rate of improvement, shortens hospital stay and lessens the risk of suicide. Karagulla, by omitting deaths and combining cases that recovered with those that improved, found that the percentage of recovery did not vary greatly whether conservative therapy or ECT was used, and further concluded that ECT did not shorten the duration of hospitalization to any significant degree. Slater (1951) soon criticized these conclusions, observing that Karagulla's data revealed (1) a much higher mortality in the untreated than the treated group (2) a significantly higher percentage of recoveries in the treated versus the untreated groups and (3) a substantially lower proportion of unimproved cases in patients admitted during the years 1900-1939. Accordingly he observed that a more careful examination of the data suggested that the exact contraries of both Karagulla's propositions were correct.

In regard to readmissions, Karagulla found their frequency was dependent on two factors (1) the length of the period through which patients had been traced and (2) the number of previous admissions. Although the relapse rates in the ECT and control groups differed in the first year following discharge, after that time no matter which group the patients had been in, the number of relapses had a direct relationship to the chronological period during which they were followed up. In a similar manner the percentage of relapse was found to increase pari passu with every subsequent readmission. Seeking to explain the slightly higher percentage of relapse in the first six months in patients treated with ECT, Karagulla drew

attention to the higher percentage of ECT cases discharged "recovered" in the treated group (56.4%) versus the control group (46.8%). This might be due, she postulated, to ECT inducing in some cases a false sense of well being. "In this state of mild euphoria" Karagulla wrote "the patient tends to assert (her) sense of well being and demands to be discharged. This mood is short lived, hence the greater tendency to relapse in treated cases in the first six months after discharge as compared to cases that recovered spontaneously".

In 1954 Thomas reported some interesting findings in a group of 307 patients with depressive states treated with ECT. He divided depressive syndromes in patients who, after the completion of ECT, again became ill into two groups (1) relapses - a need for further treatment within four weeks of the last ECT and (2) recurrences - any worsening of condition calling for further ECT, readmission, admission to another hospital or leading to suicide occurring more than four weeks after the patient's last ECT. In 74 per cent of his cases, recovery was smooth and uneventful, but in 98 per cent of the remainder a relapse or "interruption of recovery" occurred within 16 days of the cessation of treatment. Their subsequent rate of recurrence was 41 per cent as opposed to 16 per cent in patients who had achieved an uninterrupted recovery. Thirteen months after the final ECT the overall recurrence rate was 23 per cent, although the rates for certain types of depression were somewhat higher (agitated depression 41%, involutional depression 38% and depression with hypochondriasis 33%). In a controlled trial of ECT and iproniazid in the treatment of endogenous depressions, Kiloh, Child and Latner (1960) also found a high relapse rate with ECT; of their 52 cases treated with ECT, 94 per cent showed a good immediate response but in the course of six months 48 per cent relapsed, many of them within two or three

weeks following the cessation of treatment.

In table 1, it will be noticed that the majority of the 2028 patients were women with psychotic depressive states, either manic depressive depressions or involutional melancholias. In general in the earlier studies with seven or more convulsions administered per patient and a fairly long period of hospitalization - three months or more - the response rate is high (80% or more) and the relapse rate is low (8 -17%). Studies in which fewer treatments have been given, as that of Thomas (1954), or in which hospital stay has been unduly short (Huston and Locher 1948b), have shown considerably higher rates of relapse (23% and 31% respectively). Kiloh, Child and Latner's study probably falls into the latter category though, since they do not state either the average number of ECT's given or the period of hospital stay, it is difficult to be certain of this. In general the finding is consistent both with the author's personal experience and with some E.E.G. findings reported by Roth. Given eight or nine treatments, fewer of the author's depressed cases relapsed than others given five or six (Nordern 1956). Roth (1952) was able to correlate response to ECT with the release of paroxysmal bilaterally synchronous two to three per second slow waves appearing in the thiopentone E.E.G., after the third treatment: he found that the duration of such activity steadily increased to a maximum of 150-200 seconds after seven to nine convulsions. This duration of delta discharge must, in general, be reached (by giving seven to nine convulsions) if subsequent relapses are to be kept to a minimum (Roth 1956).

LEUCOTOMY

Prefrontal leucotomy, which was introduced by Moniz in 1935, was originally regarded with some distaste by many, for the early "classical" forms of the operation, by permanently damaging large areas of the brain, not infrequently led to deterioration of the personality and troublesome post-operative epilepsy. Nevertheless, with the advent of more anatomically restricted techniques which have almost completely obviated the undesirable sequelae of the classical procedure, the operation has come to be viewed with more favour. The published results leave little doubt that, amongst other disorders, depressive states, especially of the endogenous variety, respond well to this treatment. Chronic intractable depressions have generally been the cases subjected to leucotomy, as well as patients with recurrent depressive episodes, whose recovery with ECT has been too transient for appreciable benefit.

In an early investigation Partridge (1949) studied 82 patients with affective disorders out of a total of 300 subjected to prefrontal leucotomy. In general, the results were good; of 61 endogenous cases, 20 showed post-operative persistence of symptoms and relapse occurred in 4; of 21 reactive cases, none showed post-operative persistence of symptoms but relapse also occurred in 4. Partridge's conclusion from these findings was that reactivity carried a more favourable prognosis with regard to the operation, but that it also implied a greater chance of subsequent relapse. A few years later Freeman (1957) in the United States, reported a study of 3,000 lobotomized patients followed up for one to twenty years; for involutional depressives his response rates (as measured by the patient being out of hospital and at home) were 80 per cent for classical prefrontal

lobotomy and 90 per cent for the transorbital operation. With the latter technique there was, Freeman found, a much lower incidence both of post-operative personality change and convulsive disorder. Meanwhile, in England a year earlier, Elithorn and Slater (1956) had conducted a follow-up questionnaire enquiry into the views of 103 patients who had undergone pre-frontal leucotomy; 66 said that they were glad they had had the operation, and 72 of 93 relatives thought the patients were better off.

Elithorn (1958) subsequently concluded that leucotomy was most beneficial when the depression was autonomous or secondary to a genuine disability. A year later, an investigation carried out by Thorpe (1959) into the 5-9 year follow-up results of limited leucotomy in patients over 65, 46 of whom had had depressive illnesses, also showed how beneficial leucotomy could be. Thorpe concluded, on the basis of his findings, that lower quadrant leucotomy was an effective treatment for intractable or recurrent, severe melancholic states; at least two thirds of patients with such conditions could, he believed, recover completely as a result of the operation and could survive for at least five years without relapse.

According to Mayer Gross, Slater and Roth (1960), however, the part that leucotomy or similar operative procedures can play in the treatment of affective psychoses, is still not yet fully explored, though they believe that there can be no doubt that leucotomy can often rapidly terminate a depressive episode. They state that leucotomy should only be employed when convulsive therapy has failed and the outlook appears hopeless without it. In this connection some figures furnished by Tooth and Newton (1961) on leucotomy in England and Wales between 1942 and 1954 are of particular interest.

Tooth and Newton undertook their survey in early 1956; between May of that year and December of the following year they sent out questionnaires which eventually yielded data on 10,365 patients who had undergone leucotomy between 1942 and 1954. 2637 of these patients, 794 men and 1834 women, had had the operation performed for amelioration of affective psychoses, illnesses in which the operation achieved its best results. Seven per cent of these patients were under 35; 80 per cent were aged between 35 and 65 and the remainder were older still. In 79 per cent, the standard operation had been performed; 11 per cent had had a modified standard operation; and 10 per cent had undergone some other surgical manoeuvre. Twenty per cent of the men and 21 per cent of the women had had a depressive illness of less than 2 years duration; 43 per cent of both sexes had had their psychoses for 2 to 6 years; 16 per cent of men and 14 per cent of women had been ill for 7 to 11 years; and the remainder had been disabled for an even longer period. Despite this, 63 per cent of the men and 69 per cent of the women had been discharged - indeed, in all, 49 per cent left hospital within one year of the operation; 20 per cent of men and 22 per cent of women had remained in hospital; and 17 per cent and 9 per cent respectively had died in hospital. Total recovery was achieved by 24 per cent of the men and 29 per cent of the women; social recovery (with residence at home) had occurred in 23 per cent of both sexes; and great improvement had taken place in 13 per cent of men and 12 per cent of women. These figures were obtained at the price of serious post operative side effects (mainly personality change from damage to the frontal lobes) in 2.1 per cent of patients and persistent post-operative epilepsy in 1.3 per cent. The overall relapse rate was 18 per cent; relapses, in general, were higher in patients in the younger age groups. In passing, the report

observes that though the level of leucotomy in England and Wales between 1948 and 1955 was running at approximately 1000 cases per annum, by 1959 the number had dwindled to 400 patients annually.

In regard to the way in which leucotomy exerts its effect, Roth and Garside (1962) have pointed out that, like electroconvulsive therapy, the operation interferes with the thalamo-frontal association pathways; the interference is, they think, temporary with electroconvulsive treatment, but permanent with leucotomy. Roth and Garside remark how great would be the advance registered by the introduction of a form of treatment less transient in its effects than electroconvulsive therapy, yet less irrevocable than operations on the frontal lobes. Today, antidepressant and tranquillizing drugs should be given a full trial before leucotomy is considered. Despite the advances these new measures represent, however, Sargant (1962), in a discussion of the present indications for leucotomy, still finds room, in certain depressive states, for the modified operation providing the previous personality has been adequate. Pippard (1962), after pointing out that the decline in the number of leucotomies has been confined to the use of the standard operation, also indicates that he feels that leucotomy can be of value, amongst other disorders , in persistent depressive states in the elderly and that, at the present time leucotomy is probably underused.

THE TREATMENT OF DEPRESSION WITH DRUGS

The use of drugs in psychiatry, as Marley (1959) has pointed out, can be traced back to the dawn of Western Civilization. "The Greeks" Marley states, "made good use of the pharmacopoeia, prescribing borage, bugloss, marigold, polypodie and epithyme for melancholy, more specifically recommending wormwood, centaury and pennyroyal for the hypochondriac malady".

Burton, in his "Anatomy of Melancholy", first published in 1621, described the use of black hellebore and other purges, whilst other writers living in Burton's era, such as Culpeper, recommended plant and herbal remedies for depressive states. Such remedies were of a non-specific nature, and the modern era of pharmacotherapy for depression began in 1936 when Peoples and Guttman in the United Kingdom, and Myerson in the United States, began to use amphetamines in depressive illnesses. The antidepressant compounds currently in use (or in use at some time since 1936) are shown in Table 2, which is adapted from a table contained in a review by Cole, Jones and Klerman (1961).

TABLE 2 - ANTIDEPRESSANT DRUGS

GENERAL CLASSIFICATION	GENERIC NAME	TRADE NAME
(1) PSYCHOMOTOR STIMULANTS		
A. Amphetamines	amphetamine	Benzedrine
	dextroamphetamine	Dexedrine
	methamphetamine	Methedrine
B. Amphetamine-like	phenmetrazine	Preludin
C. Non-amphetamines	methylphenidate	Ritalin
	pipradrol	Meratran
	deanol	Deaner
(2) MAO INHIBITORS	iproniazid	Marsilid
A. Hydrazines	pheniprazine	Catron
	isocarboxazid	Marplan
	nialamide	Niamid
	phenelzine	Nardil
B. Non-hydrazine	erytryptamine	Monase
	tranylcypromine	Parnate
(3) IMINODIBENZYL DERIVATIVES		
	imipramine	Tofranil
	amitriptyline	Tryptanol

(1) PSYCHOMOTOR STIMULANTS.

Amphetamine compounds have little effect in severe states of depression. Accordingly, these drugs have, in the main, been used in the treatment of milder "neurotic" or "reactive" cases on an outpatient basis. Unfortunately, though in general they engender euphoria, increase alertness and lessen fatigue, in a proportion of patients they produce increasing anxiety, agitation and despair. Their side effects include dryness of the mouth, palpitations, anorexia and insomnia; but since, Rees (1960) points out, their mood-elevating effect is often short-lived and succeeded by an intensified state of irritability, fatigue and dejection, and since toleration quickly develops, the physician prescribing amphetamines not infrequently finds he has to administer them in steadily increasing quantities in order to continue to obtain good results. Combinations of amphetamines with barbiturates (such as "Drinamyl", which is dextroamphetamine 5 mg. with amylobarbitone grs. ½) have mitigated amphetamine side effects to some degree, but have not minimized the chief hazard of their use - addiction. This problem, a serious and not very infrequent complication of amphetamine treatment, has received an increasing amount of attention of late (Connell 1958, Bell and Trethowan 1961, McCormick 1962). Phenmetrazine ("Preludin"), a related compound, through its use as an anorexogenic agent and euphoriant, has also led to addiction and toxic psychoses (Bartholomew and Marley 1959).

Amongst other non-amphetamine stimulants which have proved of limited usefulness are methylphenidate ("Ritalin"), pipradrol ("Meratran") and deanol ("Deaner"). Though methylphenidate antagonizes reserpine and promotes alertness, a blind controlled trial has shown that it is no better than placebo (Robin and Wiseberg 1958). Pipradrol did not live up to the expectations of Fabing, Hawkins and Moulton (1955), and deanol, the third compound

mentioned, has also, in a double blind self-controlled clinical trial, been shown to be ineffective (Dominion 1960). On the other hand, a proprietary combination tablet of benactyzine (1 mg.) and meprobamate (400 mg.), "Deprol", has been shown to be of value in mild neurotic depressions, though whether this relief is due to one or other constituent, or both together, remains uncertain (Cole, Jones and Klerman 1961).

(2) MAO INHIBITORS

IPRONIAZID

The first major breakthrough in the drug treatment of depression was the introduction of iproniazid ("Marsilid") in the mid 1950's. Two papers by Kline and his associates (1957) and Crane (1957) given at an American Psychiatric Association Conference at Syracuse "set off", Cole et al. (1961) remark, "the current frenzy of clinical, pharmacological and biochemical research." "The significance of these reports", they percipiently go on to state, "was not so much their claims for therapeutic effects, but the linkage of clinical action to enzymatic inhibition." The same year saw a second major breakthrough in the treatment of depression - the introduction of the iminodibenzyl derivative imipramine ("Tofranil") by Kuhn (1957). Parenthetically it is interesting to note that the development of the two major groups of antidepressants, the amine oxidase inhibitors and the iminodibenzyl derivatives, of which iproniazid and imipramine were the forerunners, was foreshadowed by the successful treatment of schizophrenia with reserpine and chlorpromazine in 1954 and 1952 respectively. As with convulsion therapy, history would seem to have repeated itself.

Kline (1958) has described how his success with reserpine in schizophrenia led him to attempt the treatment of withdrawn and depressed

patients with iproniazid. Iproniazid's parent compound isoniazid had earlier been shown to be of value in the treatment of tuberculous patients, in whom it produced euphoria and gain in weight, an action at first mistakenly attributed to improvement in the pulmonary circulation. Isoniazid actually underwent preliminary trials as an antidepressant (Delay and Buisson 1952), but together with its daughter compound iproniazid was abandoned as too toxic for clinical use. Nevertheless Kline, visiting his laboratory one day, was struck by the observation, made by one his associates, that animals pre-treated with iproniazid did not become sedated when given reserpine. It was this antagonism between reserpine, which he knew tranquillized schizophrenics, and iproniazid, that encouraged Kline to try the latter drug in depressives. Later, parallels between clinical efficacy and the property of monoamine oxidase inhibition encouraged theoretical explanations of iproniazid's antidepressant action as being due to the latter property.

Despite the fact that iproniazid has been in use longer than any other effective antidepressant, the papers describing the clinical actions of the drug are, by and large, Cole et al. (1961) point out, inferior to those on imipramine. Early reports suggested that response to this compound, when it occurred, was dramatic and striking. Some authors felt that iproniazid was better in psychotic than neurotic depressions while others, notably West and Dally (1959) found that atypical, primarily neurotic, depressives responded best. More recently, several controlled trials have been carried out in which iproniazid has been compared with psychotherapy, placebo or ECT (Cole, Patterson, Craig, Thomas, Ristine, Stahly and Passamanick 1959; West and Dally 1959; Rees and Benaim 1960; Kiloh, Child and Latner 1960 a,b; and Wittenborn, Plante, Burgess and Livermore 1961). The available evidence seems to suggest that while iproniazid is not, in

general, as effective as ECT, it is of value in alleviating the acute symptoms of a proportion of severe depressives and of a larger proportion of mild cases. It is also effective in maintenance therapy, as shown in table 3 which, amongst other trials, summarizes the only followed-up blind controlled iproniazid study to appear in print. Unfortunately, the drug has several dangerous side effects, of which the commonest is hepatitis; thus Cares and Buckman (1961) list 17 deaths from hepatic necrosis following iproniazid therapy, and other complications include mania, orthostatic hypotension, peripheral neuropathy, oedema, hyperreflexia, impotence, dizziness, blurred vision, insomnia, dry mouth and constipation. Because of these side effects, iproniazid has lost ground to the newer MAO inhibitors and imipramine, and now is seldom used in clinical practice (Hordern and Somerville 1962).

THE NEWER MAO INHIBITORS.

The newer MAO inhibitors however, whilst somewhat safer, have not so far shown themselves to be convincingly more efficacious than iproniazid, their parent compound. In this connection Cole et al. (1961), who base their opinion on the evidence provided by a large number of clinical reports, summarize the position as follows:- "It seems reasonably certain that the MAO inhibitors are potent and effective drugs, whose actions cannot be explained solely on the basis of placebo effect, suggestion, added care or social effects. Pharmacologically they are different from, and clinically they are superior to, the traditional psychomotor stimulants such as amphetamine, methylphenidate or pipradrol. Most observers seem agreed that their slow onset of action precludes their use in severely depressed patients, especially where suicidal tendencies are strong. Practically no clinicians feel that the results of treatment with MAO inhibitors surpass

those with ECT. Iproniazid remains the standard of comparison. Although the newer compounds are more active pharmacologically in animal studies than iproniazid, there is little evidence that a larger proportion of patients are improved, or that the quality of improvement is superior to, or even very different from that obtained with iproniazid. The new compounds do offer fewer adverse effects and less danger of serious complications; whether they offer added clinical efficacy remains to be proved."

Increasing experience with MAO inhibitors has shown that these drugs can have adverse effects if indiscriminately combined with other medications. They potentiate opiates, atropine derivatives, barbiturates, ganglionic blocking agents, corticosteroids and anti-rheumatic compounds; they enhance the hypotensive effects of chlorothiazide and hydrochlorothiazide; and they sensitize patients to the release of histamine, to novocaine and anaesthetic agents. Phenelzine can cause hypotension (Davies 1960); excruciating headaches, combined with constricting sensations in the chest, tachycardia and palpitations, have occurred when methylamphetamine has been given intravenously to patients who have been on MAO inhibitors (Dally 1962). A combination of amphetamine and tranylcypromine has caused death on more than one occasion (Zeck 1961, Mason 1962), the usual pre-mortem diagnosis being subarachnoid haemorrhage or phaeochromocytoma. Ayd (1961 b) has pointed out that the effects of MAO inhibitors persist after cessation of the drug, so that it is wise to wait at least a week after discontinuance of a MAO inhibitor before giving imipramine or amitriptyline; for this reason the treatment of a severe depression should probably always commence with an imino-dibenzyl derivative.

PHENIPRAZINE AND ERYTRYPTAMINE.

Pheniprazine ("Catron") was found to be of the same order of effectiveness as iproniazid in a blind trial carried out by Crisp, Hays and Carter (1961). Unfortunately the compound was toxic and following Beer and Schaffner's (1959) report of red-green colour blindness and severe hepatitis, pheniprazine was generally withdrawn from world markets. Erytryptamine ("Monase"), another recently-developed MAO inhibitor, has also been withdrawn because of toxicity and iproniazid itself was omitted from a selective list of psychiatric medications issued in Washington D.C. in 1962 by the Psychopharmacology Service Center.

ISOCARBOXAZID.

Isocarboxazid ("Marplan"), an analogue of iproniazid, is safer than the older drug, and has been shown to be more effective than placebo in the treatment of depressive syndromes (Rothman, Grayson and Ferguson 1961a). According to a second study carried out by the same authors, it may alleviate depression in a way that differs from imipramine, which they also find to be an effective antidepressant (Rothman, Grayson and Ferguson 1961b). Unfortunately, the value of these two carefully performed blind studies is limited by the small numbers of patients completing them, and also by the inclusion of cases belonging to such varied diagnostic categories as schizophrenia, schizo-affective state, depression and personality disorder. A similar shortcoming - that of including a large, heterogeneous group of "secondary" depressives - is evident in a third controlled trial in which isocarboxazid was compared with placebo: 50 per cent of 26 patients on isocarboxazid were improved or markedly improved after 30 mg. of isocarboxazid daily for three months in contrast to 10 per cent improving on placebo (Joshi 1961). In this trial, depressives in general responded well

to isocarboxazid, particularly secondary depressions accompanied by agitation in elderly patients, but psychoneurotic depressives did not do so well, and severe and recurrent endogenous depressives were not helped at all. None of the three studies, therefore, suggests that isocarboxazid is unusually effective in the treatment of depressive syndromes. In connection with the clinical value of isocarboxazid Cole et al. (1961) pertinently remarks, "Although most clinicians are agreed that it is safer than iproniazid, almost none feel that its clinical effectiveness is greater than the original MAO inhibitor or ECT. However, in the hands of clinicians experienced in the use of more than one MAO inhibitor, the compound appears to be more potent than nialamide and safer than phenylisopropylhydrazine and iproniazid. At this point, however, it is impossible to ascertain whether it is clinically more effective than phenelzine or ECT."

NIALAMIDE.

Nialamide ("Niamid"), also more potent pharmacologically than iproniazid, seemed promising at first because it did not produce the hypotensive side effects of the older compound. It has, in general, turned out to be less effective than other MAO inhibitors, though in one recent controlled trial in chronic depressives, nialamide was more effective than iproniazid and pheniprazine, ranking second only to phenelzine; patients under 40 responded best to the drug (Bates and Douglas 1961). On the other hand, a blind trial carried out in 50 hospitalized depressives, in which nialamide was compared to chlorpromazine, showed no significant difference between the improvement rates of patients treated with either compound. Though, after two weeks the improvement rate was 77 per cent for nialamide and 67 per cent for chlorpromazine, at the completion of the trial four weeks

later, the respective improvement rates had dwindled to 50 per cent and 42 per cent (Affleck, Forrest and Martin 1961). In summary therefore, Cole et al's. (1961) statement appears to provide an accurate estimate of the value of nialamide: "It is probably less toxic, and also less effective, in the treatment of severe depressions than most of the other MAO inhibitors."

PHENELZINE.

Phenelzine ("Nardil") is a further MAO inhibitor which, chemically, is closer to pheniprazine than iproniazid. Although the compound has the advantage of being relatively safe, an early controlled trial carried out by King (1959), in which 25 severely depressed patients were randomly assigned to phenelzine or ECT, revealed that the drug was far inferior to electroconvulsive treatment. A brief blind controlled trial of phenelzine in hospitalized female depressives, carried out by Harris and Robin (1960), showed no advantage for the drug over placebo, but other trials have given more promising results. Thus, Hutchinson and Smedberg (1960) found phenelzine significantly better than placebo in a double blind cross-over trial on 34 hospitalized female depressives; the trial lasted six weeks, of which four were occupied in giving the active drug. As mentioned earlier, Bates and Douglas (1961) found phenelzine superior to pheniprazine, iproniazid and nialamide in the treatment of 54 depressives. Rees and Davies (1961), in a triple-blind, self-controlled trial carried out on 20 hospitalized depressives, gave phenelzine and placebo randomly for two three-week intervals; they found that 50 per cent of phenelzine-treated patients recovered completely, or improved markedly, in contrast to 15 per cent responding similarly to placebo ($p < .05$). However, 13 of the 20 patients still required ECT to effect a complete recovery, and Rees and Davies state: "there can be no doubt that the drug is not as effective as

ECT for severe depressive illness." A more recent trial carried out by Hare, Dominion and Sharpe (1962), compared phenelzine with dextroamphetamine sulphate and placebo in 43 moderately depressed patients, 4 of which were in-patients, while the others were attending a day hospital. Drugs were given for two weeks and the assessments were subjected to sequential analysis. On the clinical manifestations of depression, neither phenelzine nor dextro-amphetamine were better than lactose, but phenelzine was significantly better than both other compounds in alleviating agitation and anxiety. In summary, therefore, it seems that, while phenelzine is not as effective in severe depressives as ECT, it is at least as potent, if not more so than iproniazid, and is more effective than nialamide (Cole et al. 1961).

TRANYLCYPROMINE.

Tranylcypromine ("Parnate") is a non-hydrazine MAO inhibitor which chemically resembles amphetamine. The MAO inhibitor activity of this compound, unlike its predecessors, appears rapidly and lasts only a brief time (Tedeschi et al, 1959). This property, together with absence of the hydrazine moiety, has been claimed to make the compound safer than other MAO inhibitors in clinical use. Enthusiastic early reports describing the rapid clinical improvement effected by tranylcypromine have been substantiated by a con-trolled trial in which it was compared to placebo in out-patient depressives. Bartholomew (1962) gave 30 mg. of tranylcypromine daily for two weeks, followed by 60 mg. of the compound for four more weeks; overall, the results indicated that tranylcypromine was superior to placebo at the 5 per cent level, though no significant superiority could be demonstrated in the treat-ment of either endogenous or involutional depressions. Bartholomew concluded that tranylcypromine was of most value in the treatment of the milder or reactive depressive states. The effect of the drug may, Cole et al.

believe, be related to an amphetamine-like stimulating action which can lead to troublesome and dangerous side effects. As mentioned earlier, spasmodic hypertension has occurred, causing severe occipital headaches leading to a diagnosis of subarachnoid hypertension or phaeochromocytoma. At least two deaths have occurred from giving a combination of tranylcypromine and amphetamine, either orally (Zeck 1961) or intravenously, as an abreagent (Mason 1962). Because of the disadvantage of tranylcypromine's side effects, a combination of 10 mg. of this compound with 1 mg. trifluoperazine has now been prepared, which is available for use under the trade name "Parstelin".

(3) IMINODIBENZYL DERIVATIVES.

IMIPRAMINE.

Imipramine ("Tofranil") was synthesized in 1948 in the Geigy Laboratories in Switzerland in the course of work on the development of sedatives, antihistaminic and antiparkinsonian agents. Imipramine is not a monoamine oxidase inhibitor; indeed, chemically it resembles chlorpromazine ("Largactil"). Kuhn carried out preliminary trials with imipramine as long ago as 1950, but the drug was shelved until 1954, when interest was rekindled by the realization that its action in potentiating narcosis and producing artificial hibernation paralleled that of chlorpromazine; the latter compound, because of its effectiveness in schizophrenia, was at that time very much in the psychiatric eye. In the next three years Kuhn (1957, 1958) treated 500 psychiatric patients with imipramine, thinking that it, too, might be of benefit in schizophrenic patients; nevertheless he discovered that depressives rather than schizophrenics showed a beneficial response. Indeed, 75 - 80 per cent of endogenous depressives improved as a result of administration of the drug; moreover, he obtained good results in reactive depressives as well. In 1958, imipramine became generally available

in Europe; a year later, through the medium of a Conference on Depression and Allied States held at McGill University, Montreal, it was introduced to North America. A great many impressionistic studies soon appeared but, as usual, adequately controlled trials were not very numerous. An increasing amount of clinical experience, however, began to show that imipramine was superior to the MAO inhibitors in the treatment of severe depressive states. Thus, in 1960, a reviewer wrote, "Iproniazid ("Marsilid") seemed at first to give ECT some competition but its side effects proved too hazardous for its general use. Imipramine ("Tofranil") has edged iproniazid out of the running as a substitute for ECT ....." (Wilcox 1960).

TABLE 3.

RESULTS OF SOME BLIND CONTROLLED DRUG TRIALS ON DEPRESSED PATIENTS

DRUG	Mean Daily Dose	PERIOD GIVEN	NUMBER & TYPE OF PATIENTS E = endogenous R = reactive	PERCENTAGE RESPONSE		REMARKS	SOURCE
				DRUG	CONTROL PATIENTS		
Iproniazid "Marsilid"	150mg	3 weeks+	26 E. depressed in-patients	54%	11% of 25 on placebo 89% of 27 on E. C. T.	Follow-up carried out to assess relapses.	Kiloh, Child & Latner 1960a.
Iproniazid "Marsilid"	?	6 months	30 E. depressed in-patients	40%	48% of 52 on E. C. T.	6 months relapse rates on iproniazid 14%, E. C. T. 40%.	Kiloh, Child & Latner 1960b.
Imipramine "Tofranil"	250mg	1 month	27 E. and 22 R. depressed out-patients.	74%E 59%R	22% of 28 on placebo 20% of 20 on placebo	Very severe cases excluded. Side effects ++. Follow up carried out to assess relapses.	Ball & Kiloh 1959.
Imipramine "Tofranil"	100mg	6 months	27 E. and 22 R. depressed out-patients	48%E 41%R	48% of 52 on E. C. T. (from earlier study)	6 months relapse rate. 18% in endogenous cases, 66% of who had responded. Side effects ++	Kiloh & Ball 1961.
Imipramine "Tofranil"	200mg	6 weeks	38 of 62 depressed in-patients.	60%	25% of 24 on placebo	Psychotic depressives did as well as neurotics. Side effects trivial.	Kenning, Richardson & Tucker 1960.
Imipramine "Tofranil"	225mg	4-6 weeks	50 depressed in-patients	65%	21% of patients on placebo	Deluded & severely ill patients did poorly. Side effects +	Friedman, Mowbray & Hamilton 1961.
Imipramine "Tofranil"	250mg	2-3 weeks	20 severely depressed in-patients	35%	10% of 20 on placebo	Patients used as own controls. Only severe cases included. Side effects +	Rees, Brown & Benheim 1961.

Table 3 summarizes the salient features of a number of blind controlled trials of iproniazid and imipramine, prior to amitriptyline the most effective antidepressant medications. Ball and Kiloh's imipramine trial has the merit of having been carried out on an adequate number of patients who were all "pure" depressives; their study was well followed up and has provided the basis for many subsequent comparisons. Two aspects of Ball and Kiloh's investigation should, perhaps, be especially emphasized, both arising from the fact that it was carried out on out-patients:- (1) Very severely agitated, and/or depressed patients who required ECT were excluded; thus few patients with overt depressive delusions were admitted to the trial (2) Side-effects were found to constitute a considerable problem. The commonest were dry mouth, sweating, constipation, faintness, dizziness, nausea, vomiting, shakiness and tremor. Insomnia, malaise, blurred vision and an unpleasant taste in the mouth also occurred. One patient developed grand mal epilepsy and one became hypomanic. Overall, side effects of some degree were present in 83 per cent of cases.

The trial carried out by Kenning, Richardson and Tucker is significant, for it was the earliest blind adequately-controlled study in which an attempt was made to establish whether or not imipramine possessed a specific effect over and above hospitalization and other non-specific agents. Sixty per cent of the imipramine treated patients responded and side effects were noted to be unusually mild. A similar order of response was found in a second trial conducted on in-patients by Friedman, Mowbray and Hamilton (1961). Though deluded patients in particular did not respond to imipramine, the overall response rate to the drug was 65 per cent; side effects did not constitute a problem. Finally, in table 3, the investigation carried out by Rees, Brown and Benaim merits scrutiny, for it

was conducted on 20 unusually severe hospitalized depressives; their response to imipramine was 35 per cent, in contrast to a response rate of 10 per cent to placebo. Again, side effects did not constitute a real problem.

The trials summarized in table 3 have been specially selected, since it is considered that each has particular relevance to an investigation of the efficacy of amitriptyline in hospitalized depressives. The iproniazid trial conducted by Kiloh, Child and Latner demonstrates that the results obtained with this, rather toxic, compound are not as good as those obtained with imipramine. Ball and Kiloh's trial of imipramine shows that good results, both immediate and after six months, can be obtained with imipramine, though side effects can be a troublesome complication of treatment. Kenning et al's. trial shows that the results produced by imipramine in in-patients are not quite as good as those obtained in out-patients (60% vs. 66%), though side effects in in-patients are much less troublesome. These findings are supported by the investigation conducted by Friedman et al.; and finally, the last trial on table 3 shows that if the administration of imipramine is confined to severe depressives, the response rate is lower still - of the order of 35 per cent.

In all these trials, the methods by which patients were evaluated are of interest, for evidence will later be presented that valuable information may be missed if imprecise instruments are used. Kiloh, Child and Latner, and Kiloh and Ball employed five-point clinical assessments. Kenning et al. relied on clinical appraisals, the Wittenborn scale and a number of psychological tests. Friedman et al. used a 25 item questionnaire, a five-point scale based on an instrument constructed by

Shapiro, and the depression sub-scale of the Wittenborn Rating scale. Rees et al. graded clinical features on a five-point scale, also using nurses' observations and weekly overall physicians' gradings of their patients' state.

Before leaving imipramine, a number of other trials less relevant in the present connection, merit brief mention. One of the first trials reported was that of Lehmann, Cahn and de Verteuil (1958), who found that imipramine was significantly superior to placebo in averting and relieving the relapses that could be produced by deliberate omission of the drug during the period of treatment with it. Leyberg and Denmark (1959) obtained good results with imipramine in a controlled blind study on 20 clinically depressed in-patients. A further trial was carried out in 24 chronic depressives by Doust, Lewis, Miller, Sprott and Wright (1959). Patients entered this trial in replications of groups of four to receive no drug, placebo, dextroamphetamine, iproniazid and imipramine; although imipramine was administered for only one week, several patients improved.

In 1960, Holt, Wright and Hecker reported a study in which they had given imipramine, isocarboxazid, phenelzine and phenipramine to 100 hospitalised patients. All four drugs were found to be effective antidepressants, imipramine producing results comparable with phenelzine, the best drug of the four. Since no indication is given as to whether ratings were blind, and since patients in several diagnostic categories were included, the result of this trial must be interpreted with caution. Bruce, Crone, Fitzpatrick, Frewin, Gillis, Lascelles and Merskey (1961), who compared imipramine with ECT in 50 consecutive admissions (49 of whom were endogenous depressives), found that a higher percentage of patients had

responded to ECT after a month, but that 60 per cent of imipramine-treated cases also recovered. Ashby and Collins (1961) carried out a double-blind comparison of imipramine and placebo in 15 chronically depressed in-patients, each patient randomly receiving nine weeks on the drug and nine weeks on placebo. Some patients became more settled but no significant change could be detected on the rating scale that was employed. Oakley (1961), comparing imipramine with pheniprazine in a blind trial on 49 hospitalized endogenous depressives, could find no difference between the two compounds.

SUMMARY.

In summary, the data presented in the first section indicates that depressive disorders are extremely common in the majority of countries for which reliable figures are available. The incidence and prevalence of these disorders in the community is appreciably high; secondary and primary forms of the illness are frequently encountered in general practice; psychiatrists see a great many depressives; such patients form a sizeable proportion of individuals committing suicide; many depressives are admitted to general hospitals with the symptoms of physical illnesses, and depression can also present in the guise of alcohol or amphetamine addiction. Accordingly, there can be no doubt that depression is a widely prevalent disorder at every level of medical experience.

The second section reviewed the results of treating severer depressive states with convulsant techniques and surgical procedures. Electroconvulsive therapy, though safe and highly effective in most cases, has the drawback of being distasteful to patient and physician, of producing transient confusion and memory impairment and, worst of all, of being followed by an appreciable proportion of relapses - overall, these occur in

some 20-30 per cent of cases. Leucotomy, whilst very effective in severe depressive states, still seems an unduly serious and irrevocable step to take, to be avoided, if possible, in the majority of cases.

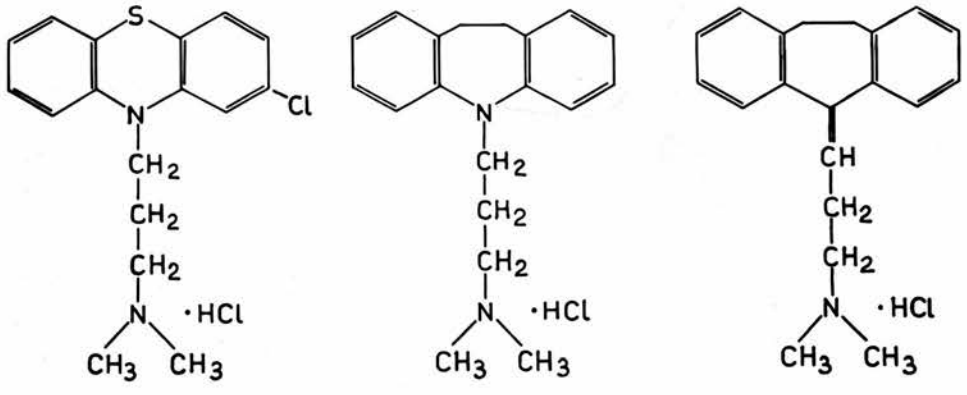
The third section, which considered the drug treatment of depressive states, presents evidence suggesting that, prior to the advent of amitriptyline, imipramine was the most effective antidepressant available for the treatment of severe depression. The trials that have been conducted indicate that, whilst improvement with imipramine does not occur as rapidly as is the case with ECT, the drug can produce results comparable with ECT some months after treatment, providing patients are kept on adequate maintenance doses. In general, the severer the depression the lower the percentage of success with imipramine; indeed, grossly depressed, overtly deluded patients have been noted to respond poorly, if at all. Side effects, it has been found, can be troublesome; in general, they have been more of a hazard in out-patients than in in-patients treated with this compound.

CHAPTER 11.

AMITRIPTYLINE IN DEPRESSIVE STATES: A CONTROLLED TRIAL

In 1960 the first clinical reports began to appear on amitriptyline ("Elavil" "Tryptizol" "Tryptanol"), a new antidepressant developed by Merck Sharp and Dohme of Philadelphia. Amitriptyline is (5 - amino - propylidine) - dibenzo (a, d) (1, 4) cycloheptadiene hydrochloride, a compound structurally similar to both imipramine and chlorpromazine. The resemblance is clearly evident in the formulae of the three compounds.

FIGURE 1.



CHLORPROMAZINE IMIPRAMINE AMITRIPTYLINE

Since amitriptyline has only recently been developed, and since no blind controlled trials have yet been reported, the pharmacological and clinical studies so far reported will be briefly reviewed.

Vernier (1961) has provided a description of the pharmacology of antidepressant agents in general, with special reference to the pharma-

codynamic actions of amitriptyline. Extensive experimentation in animals has shown that amitriptyline weakly tranquillises both the EEG and operant behaviour; the drug is a fairly powerful anticonvulsant, and possesses weak peripheral atropine - like actions; it has strong antihistaminic properties and weak antiserotonin effects. Amitriptyline produces a degree of adrenergic blockade and has a gastric antisecretory effect; it is rapidly metabolised in the body in manner similar to imipramine. According to Sabelli, Levin, Siegler and Toman (1961), in animal studies amitriptyline behaves like imipramine; the pharmacological effects of these two compounds, together with chlorpromazine and chlorprothixizine, differed quantitatively rather than qualitatively (Herr, Stewart and Charest 1961). In squirrel monkeys and rats trained on a Sidman avoidance schedule, Hanson (1961) reports that amitriptyline, like chlorpromazine and imipramine, caused loss of avoidance responding at moderate doses and produced decreased escape responses at higher doses; both amitriptyline and imipramine produced erratic responses at high doses and, like chlorpromazine, depressed behaviour. Weissman (1961) stabilized rats on a non-discriminating avoidance task; they showed a stimulant effect with d- amphetamine, which was potentiated by premedication with imipramine. The effect of pre-treatment with amitriptyline was similar, Weissman found, though its onset was more rapid and its duration shorter; on the other hand, chlorpromazine (given in a lower dose) antagonized the effect of amphetamine. According to Pletscher and Gey (1961) amitriptyline, like imipramine, does not alter monoamine oxidase metabolism in vivo in the rat brain in the way that it is altered by MAO inhibitors, reserpine and benzoquinolozine derivatives. Cairncross, Gershon and Gust (1961) state that in experiments on cat blood pressures on an animal sedated with "Nembutal", low doses of amitriptyline produced a slight pressor effect;

higher doses (1 mg. per kilogram given intravenously) produced a brief depressor response. 1 mg. of amitriptyline per kilogram given intravenously potentiated the pressor response of adrenaline and nonadrenaline, but blocked these responses when given in higher doses.

Alexander (1961a,b) has reported investigations of the effect of amitriptyline and other drugs on the human psychogalvanic reflex; he found that, in this regard, amitriptyline occupied an intermediate position between imipramine and chlorpromazine. Perception as well as mood was beneficially affected when amitriptyline was given to male neurotic depressives (Ostefeld 1961). In regard to the metabolism and excretion of amitriptyline, Hucker and Porter (1961) state that very little appears unchanged in the urine, the compound being found there as demethylated derivatives which are excreted as glucuronides.

From a clinical standpoint amitriptyline, however administered, appears to be well tolerated and to act in manner reminiscent of both imipramine and chlorpromazine. In early trials, depressions accompanied by high levels of anxiety responded well to oral doses of 75-225 mg. of amitriptyline daily; 50 mg. thrice daily was the usual dose (Dorfman 1960). Freed (1960) found that severe tension and anxiety, even in elderly patients with cerebral damage, responded well to parenteral administration of this compound; 10-15 mg. could safely be given intravenously two or three times daily. A year later Dunlop (1961a) also reported good results with parenteral amitriptyline. In 1960 Ayd went so far as to state that he believed amitriptyline to be the treatment of choice in involutional melancholia, though other types of depression also responded, an opinion with which Dunlop (1961b) concurred. Von Arnold and Foitl (1961) state

that amitriptyline is the most useful pharmacological agent currently available for the treatment of endogenous depressions; Bennet (1961a,b) also endorses its value in these conditions, though the results reported by Settel (1961) are rather less striking. Ayd (1960,1961c) is of the opinion that, following recovery, protracted maintenance therapy with amitriptyline - 3 months or more - is necessary to prevent relapse. Most reports stress the freedom from toxity and low incidence of side effects with amitriptyline, though somnolence, blurred vision, dry mouth, dyspepsia, constipation, sweating, tremor, weakness, fatigue and hypomania have all followed administration of the compound. In studies comparing amitriptyline with imipramine Ayd (1960) obtained rates of response of 79 per cent and 73 per cent respectively; Ottman and Friedman (1961), in a blind trial, obtained rates of 72 and 71 per cent; and Weiss and Pressman (1961) found that both drugs produced remission in 75 - 79 per cent of cases. In an Australian investigation of amitriptyline Rosenbaum and Gershon (1962) obtained satisfactory improvement in 75 per cent of endogenous depressives and in 50 per cent of reactive cases; they concluded that amitriptyline, whilst at least as effective as imipramine in endogenous depressives, was less effective in reactive cases. Side effects with amitriptyline were fewer, improvement was more rapid and relapses were less frequent than with imipramine.

Aside from its effectiveness in primary depressive conditions, amitriptyline has been used to good effect in the depression, anxiety and anergia that can accompany non depressive psychoses, physical illnesses and dermatoses (Barsa and Saunders 1961, Dorfman 1961, Feldman 1961, Pressman 1961, Pressman and Weiss 1961, Vaisberg and Saunders 1961, Zelcer 1961). Schuff (1961) found that amitriptyline was effective in the treatment of gastro-intestinal disorders, particularly duodenal ulcer, when anxiety was

prominent in the illness.

The findings that have been published thus suggest that amitriptyline possesses several significant advantages over earlier antidepressants. Although it has been reported to be effective in the treatment of depression, amitriptyline has not produced palpitations, restlessness, tachycardia and anorexia, the typical side effects of the amphetamine antidepressants; moreover addiction to amitriptyline does not seem likely to become a problem. As a true antidepressant resembling imipramine, amitriptyline has been found to be effective in the treatment of depression accompanied by agitation, a syndrome only partly ameliorated by chlorpromazine, the other compound to which amitriptyline is similar. Most clinical reports suggest that amitriptyline is a more effective antidepressant than the MAO inhibitors; moreover since amitriptyline does not belong to the latter group of compounds, it appears likely that its continued use will be free from the liver and bone marrow complications that have bedevilled the MAO drugs. Further, the available evidence implies that amitriptyline is at least as effective as imipramine in depression, with the added advantage of a rapidly-evident tranquillizing effect and more innocuous side effects. Finally, patients unresponsive to imipramine have been noted to respond to amitriptyline. If these conclusions are correct, amitriptyline would appear to be the most useful antidepressant thus far discovered, and one that well deserves detailed clinical investigation.

A CONTROLLED TRIAL OF AMITRIPTYLINE.

Clearly on the basis of the work presented in Chapter 1, amitriptyline's principal rival in the treatment of depressive states is imipramine. In such conditions, blind trials have demonstrated that

imipramine is significantly more effective than placebo; moreover though imipramine is not as rapid in action or as universally successful as ECT, the results of one blind well-controlled investigation suggest that after six months there is little to choose between the two methods of treatment (Kiloh and Ball 1961). Imipramine therefore is the most appropriate specific referrent agent against which to compare amitriptyline; and the findings that have been outlined render the inclusion of placebo or ECT groups unnecessary in a study of amitriptyline's effectiveness. Accordingly the investigation to be described was carried out in three phases:

(1) A double-blind comparison of the effects of amitriptyline and imipramine was made in 73 hospitalized female depressives.

(2) To confirm these findings, 64 additional patients were given the two compounds; the total sample of 137 patients was used to explore both the phenomenology of depressive states and the prognostic significance of relevant variables.

(3) A factor analysis of the initial depressive symptom scores of the 137 patients was carried out in an attempt to delineate specific depressive syndromes; in addition, relapse rates were studied during a six-month period of follow-up period.

SETTING OF THE STUDY.

The investigation was carried out at Royal Park Psychiatric Hospital, Melbourne, a 240-bed early treatment centre for psychiatric illnesses, which serves a metropolitan and rural area of approximately one

million people. The hospital is situated in parkland three miles from the centre of Melbourne. Its 140 female and 100 male patients are housed in villa type wards of 35 or fewer beds, only two of which - the admission wards for the two sexes - are locked. The staff numbers 14 physicians and 90 nurses, and the hospital is a major psychiatric teaching faculty of the University of Melbourne.

In 1961, at the time of the investigation, approximately 1,700 women were being admitted annually, 70 per cent of them as voluntary patients. Two-thirds received a full course of in-patient treatment, staying an average period of one month; the remainder, with more adverse prognoses, were transferred to longer-stay hospitals. Admissions, virtually unselected, covered the whole range of adult psychiatric disorders; in all, some 25 per cent of female admissions presented with depressive symptomatology.

FIRST PHASE OF THE STUDY: PRELIMINARY PLANNING.

In planning the study, particular attention was paid to a number of methodological points which, in the light of earlier investigations, appeared to be of considerable importance. The main principles on which the methodology of the first stage of the study was based were as follows:-

(1) Since female depressives outnumber their male counterparts, a homogenous sample of depressed female in-patients was to be assembled for investigation.

(11) To allow of valid conclusions, this sample was to be of sufficient size.

(111) Since it was recognized that neither amitriptyline nor imipramine could be expected to act as rapidly as ECT, both compounds were to be administered in sizeable doses for a longer period than was customary.

(1V) To ensure that almost identical groups of patients would be available for investigation of drug effects, patients were to be allocated to four age/severity groups, in each of which the two drugs were to be randomly administered.

(V) To discount milieu as a between-drug variable, physical surroundings, nursing care, occupational and social therapy, were to be kept uniform for all patients.

(V1) To obviate bias, blind techniques of evaluation were to be used.

(V11) To ensure greater validity, several different criteria of improvement were to be settled on.

(V111) To measure speed of change, serial assessments were to be used.

(1X) For greater accuracy, both discrete and global methods of evaluation were to be employed. Outcome in terms of discharge or ECT - a relatively objective criterion - was to be the ultimate measure of drug efficacy.

(X) To monitor progress in the early stages of the investigation, sequential techniques were to be used.

(X1) To assess the probable significance of findings, appropriate parametric and non-parametric tests were to be employed.

(X11) Provision was made for extension, if this was indicated by the preliminary findings.

With these principles in mind, a detailed protocol of the first stage of the study was formulated. Two null hypotheses were taken for disproof:-

(1) Amitriptyline is in no way superior to imipramine in the treatment of patients with depressive states, as judged by the results at one, four, and in some cases, six weeks after commencement of treatment with the two compounds.

(11) Amitriptyline produces side effects which are no less severe and troublesome than those produced by imipramine.

FIRST PHASE OF THE STUDY: METHODOLOGY

SELECTION OF PATIENTS.

Female patients were chosen since depressive states are commoner in women than in men; when the study was initiated, this was reflected in the admission of three times as many depressed women as men to Royal Park Psychiatric Hospital. Young and very old patients were rejected, the former to minimize the risk of including women with personality disorders or schizophrenia, the latter to lessen the chances of including patients with organic psychoses. Thus patients who were considered for admission to the trial were aged between 30 and 70; they had to be prepared to stay in hospital a minimum of four weeks. It was laid down that none should have had ECT in the three months preceding admission, or major antidepressant drug therapy (amitriptyline, imipramine or MAO inhibitors) within the preceding two weeks. No epileptic or leucotomized patients were taken into the trial; further, in all that were selected, their depressive illnesses had not to be complicated by severe physical disabilities such as glaucoma or decompensated cardiac, renal or hepatic disease. Finally, since many non-English-speaking migrants were admitted to Royal Park

Psychiatric Hospital, subjects for the trial were chosen from those with no severe language barrier.

Providing these initial criteria were met, consecutive patients were taken in to the trial as long as their illnesses revealed, as a primary manifestation, a persistent alteration of mood exceeding customary sadness, apparent to the examiner and constituting a major feature of the illness. This primary affective alteration had to be supported by one or more of the following features: self depreciation, hypochondriasis, retardation and/or agitation. Depressions which were clearly secondary to other psychiatric illnesses such as schizophrenia, obsessional neurosis, dementia or severe mental deficiency were excluded. Subsequently, to facilitate comparison with the work of other investigators, patients were allocated, either to the "endogenous" "psychotic" or to the "reactive" "neurotic" categories.

Potential cases for the trial were chosen at daily routine interviews of new female admissions. As a rule, suitable subjects were observed for three or four days before being taken into the trial; during this time it was possible to ensure that the trial criteria were met, and diagnosis could be established with more certainty; further, patients who were exhibiting transient situational reactions could readily be excluded without further ado. When taken into the trial, patients received full physical and psychiatric examinations; weight and blood pressure (recumbent and erect) were recorded, and laboratory tests were performed. These included haematological examinations (Hb, W.BCs and ESR), serum bromide levels, the Kline reaction, liver function tests (alkaline phosphatase, cephalin flocculation) and urinalysis. Specific factors of the psychiatric

history were noted on a form constructed for the investigation (Appendix 1); the Hobson scale (Hobson 1953) was completed, and salient features in the socio-economic background were recorded by a psychiatric social worker (Appendix 2).

CARE OF PATIENTS.

All patients were routinely assigned to one hospital medical officer and in the course of the investigation received a good deal of additional attention. Only two wards were used, to ensure that milieu influences were as uniform as possible. After as brief a period in the admission ward as their clinical condition permitted, patients taken into the trial were transferred to a pleasant, 21-bed, open convalescent villa. As soon as practicable, patients began occupational therapy; they worked in a single group in a standardised situation under the direction of the same two occupational therapists.

ALLOCATION TO GROUPS: DRUG ADMINISTRATION.

Each patient was initially evaluated by two psychiatrists on Hamilton's (1960) depressive scale, shortly to be described. On the basis of age and severity of illness (denoted by the totalled rating scale scores) - the patient was then assigned to one of four groups (1) "young mild" (aged 30-49, scale score 0-39); (11) "young severe" (aged 30-49, scale score 40-100); (111) "old mild" (aged 50-70, scale score 0-39) or (1V) "old severe" (aged 50-70, scale score 40-100). On entering the appropriate group, the patient took the first available code number for drug administration, which was carried out according to a numerical code held in the hospital pharmacy. This method was settled on so as to avoid too great a degree of dissimilarity in patients receiving the drugs; it also facilitated the study of drug effects in relation to two leading prognostic criteria - age and severity of illness. Table 4 shows the distribution of patients completing

the first stage of the investigation.

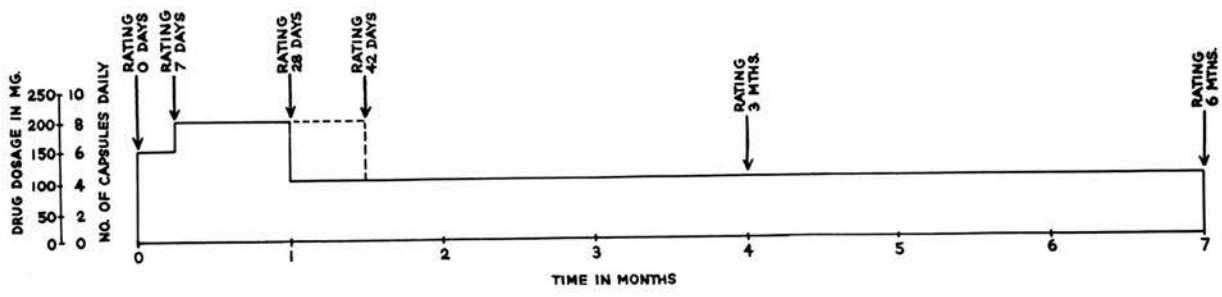
TABLE 4.

PATIENTS COMPLETING THE FIRST PHASE OF THE TRIAL (n = 73)

	"MILD" DEPRESSIVES (Scale score 0-39).		"SEVERE" DEPRESSIVES (Scale score 40-100)	
	Amitrip.	Imip.	Amitrip.	Imip.
"YOUNG" (Aged 39-49)	2	2	12	12
"OLD (Aged 50-70)	5	5	18	17

The hospital pharmacist dispensed the two drugs in identical orange capsules, each containing 25 mg.; the drug code ensured equal distribution of amitriptyline and imipramine to patients in each age/severity group. Only the pharmacist and the psychologist who evaluated the results (but was not involved in rating patients) had access to the code. The nursing staff were informed that a double blind technique was being used in the investigation; they were asked to be especially careful to see that medication was ingested, and they were specifically requested not to open capsules prior to their administration. The dosage of the two drugs was arbitrarily fixed at 150 mg. daily (i.e. 6 capsules) for one week, followed by 200 mg. daily (8 capsules) for the next three (or four) weeks. This was followed by a maintenance dose of 100 mg. daily (4 capsules) for six months. These dosage levels together with the intervals at which assessments of change were carried out, are shown in figure 2.

PLAN OF THE TRIAL



All patients were evaluated after one month of hospital treatment. At this time those who had recovered or had markedly improved were discharged on maintenance dosage; those who were unchanged were given ECT; and those who were somewhat better, but not sufficiently well to be discharged, were given a further two weeks on full dosage before a final decision was made on discharge or ECT. In 7 cases out of the first 73 - either for socio-economic reasons (5) or where a need for a further increase in weight was apparent (2) - discharge was delayed beyond these arbitrary times, and dosage was reduced to maintenance levels. Three patients who improved rapidly and wished to leave hospital were allowed home after two weeks on full dosage of the capsules; they returned for assessment as out-patients at the end of one month; their dosage was then reduced to maintenance levels.

Throughout the trial, with the exception of night sedation (sodium amylobarbitone grs. 3-6), other medication was restricted to the very occasional use of intramuscular chlorpromazine for severe agitation. ECT was never administered until patients had completed their full period of drug administration (i.e. 4 or 6 weeks), and had thus been classified as drug failures.

CLINICAL EVALUATION.

The clinical state of the patients included in the trial was blindly assessed, initially, after one week, after four weeks - and sometimes after six weeks - of drug administration. The initial evaluation provided the baseline score, i.e. the patient's condition prior to the administration of drugs. The first week evaluation was performed to see whether the tranquillizing effect claimed to be rapidly in evidence with amitriptyline,

could be detected and, if so, whether it was of prognostic significance. The four-week evaluation - or, where applicable, the six-week evaluation - was carried out to assess the results of in-patient treatment. Change in the patient's condition was registered in two "difference scores" - the difference between the initial and first week score, and the difference between the initial and final score; nevertheless, outcome, in terms of discharge or ECT, constituted the final criterion of drug efficacy.

The following methods of assessment were employed:-

(1) Rating Scale Scores: Two psychiatrists independently rated each patient on Hamilton's (1960) depressive scale at a joint interview, summing their ratings to produce a total score. This scale quantifies 17 "target symptoms" of depression; the order of its items was slightly rearranged for convenience, as shown in Appendix 3. Since an independent factor analysis was contemplated, a decision was made not to use the factors described by Hamilton. The maximum score patients could attain from the two raters was 2 X 50 = 100.

(2) Overall Clinical Assessments: The two psychiatrists who rated patients on Hamilton's scale also made independent clinical evaluations of the severity of their depressive illnesses. On these ratings, depression was registered as 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. Totalling the ratings of the two assessors gave a score range of 0 - 8.

(3) Occupational Therapy Ratings: Two independent ratings, later summed to make a total score, were made by two occupational therapists at times corresponding as closely as possible to the Hamilton scale assessments. Patients were rated during their performance, in groups of not more than six, on a series of tasks selected on the basis of

five criteria: (1) they needed only simple, clear-cut instructions and required little continued support from the occupational therapist (2) they had a definite objective (3) they required little preparation (4) they were very similar in degree of difficulty, requiring the same level of skill and (5) they were inexpensive. The chosen tasks were those involved in making covers and covering children's books for a local school. The task for rating 1 was cutting and pasting magazine pictures in montage form; rating 2 was made on candle wax painting and drawing; rating 3 was made on potato cutting and printing; and rating 4, when completed, was made on book covering, with simplified instructions.

To carry out these assessments, an occupational therapy rating scale constructed for the investigation was used (Appendix 4). The scale quantified eleven items of behaviour under task performance, depressive symptoms and interpersonal relationships. The total scale score was 33; summing the two raters' scores, gave a possible maximum score of 66.

(4) Ratings of Side Effects: These were made thrice weekly by a physician not otherwise employed in rating procedures. A scale elaborated to include the reported side effects of amitriptyline and imipramine was employed (Appendix 5). Each symptom was quantified on a four-point range of severity, and both patients and nursing staff were asked to bring side effects to the rater's attention. Since it was of paramount importance to distinguish true side effects from "side effects" which were part of the patients' depressive syndromes, initial pre-drug assessments were always made.

(5) Outcome of Treatment: Finally, amitriptyline and imipramine were compared in terms of the numbers of patients who were discharged relieved (after four to six weeks) and the numbers who had to go on to receive ECT; for comparison with the findings of other investigators, outcome according to category of depression was also computed.

PRELIMINARY FINDINGS

SELECTION OF THE FIRST 74 PATIENTS.

Although, as was earlier pointed out, depressive states occur very frequently, and constitute an appreciable percentage of female admissions to Royal Park Psychiatric Hospital, six months passed before 74 patients were collected who conformed to the designated criteria. During this period (June - December, 1961) 800 female patients were admitted, some 250 of whom presented with depressive symptomatology. Of those who were rejected, 21 per cent had had recent major antidepressant drug therapy, 19 per cent responded rapidly to the hospital environment, 15 per cent were outside the age range, 15 per cent had depression "secondary" to other illnesses (principally schizophrenia), 13 per cent had had recent ECT, 11 per cent had too severe a language barrier to allow of valid ratings, and 6 per cent were suffering from associated physical disorders.

SOCIO-ECONOMIC BACKGROUND.

In socio-economic background, as was to be expected from the method of allocation to the drugs, there was no significant difference between the two groups of patients. Of 73 patients included in the first phase of the study (one of the first 74 died) 85 per cent had been born in Australia; their mean age was 52.0 with a standard deviation of 10.85 years.

Eighty-six per cent were, or had been, married, and the majority of these had one, two or three children. Only 8 per cent had progressed beyond the primary school level and, for most, vocational qualifications were restricted to semi-skilled industrial and clerical work. Most were housewives; all 15 per cent who worked were employees. Precise figures in regard to income were not obtained, but it is known that 45 per cent depended on their husband's earnings, 34 per cent on pensions, and 11 per cent on their own earnings. Sixty-two per cent lived in dwellings which they owned or were paying for; the remainder lived in rented houses or flats. The socio-economic profile was of a predominantly lower-middle class group with an assured but usually low income and generally low levels of education, vocational training and experience.

PSYCHIATRIC BACKGROUND.

In psychiatric background, likewise, there were no significant differences between the patients in the two drug groups. Of the 73 patients, 46 per cent had never been previously hospitalized for mental illness; 25 per cent had been in hospital only once before and 29 per cent had been hospitalized two or more times. Sixty-two per cent had first required medical attention for their condition within the preceding two years; 12 per cent had needed help between three and five years before their current illnesses and 24 per cent had had to seek assistance between six and twenty years previously. Ten per cent had received antidepressant therapy (within the specified limits) prior to admission; 6 patients had been given drugs, whilst 1 had had ECT. One patient had developed her depressive state within a week, but in 76 per cent the illness had taken one to eight weeks to develop; in 23 per cent of cases the depression had come on more insidiously.

In 52 per cent of patients, no precipitants could be found; in 33 per cent, however, psychological stresses were in evidence and had apparently precipitated the illness. These included domestic anxieties, such as grief, problems with children or -in-laws, or more general stresses such as anxiety after car accidents or prior to impending surgery. In the remaining 25 per cent of patients, physical precipitants were in evidence - alcohol, gynaecological conditions, hypertension, influenza, operations, the puerperium and the ingestion of reserpine.

LABORATORY FINDINGS.

No significant alteration in blood pressure or other somatic functions were noted during the trial and both drugs, in general, seemed safe and non-toxic in the doses that were used. Nevertheless, one 65 year-old patient died on the 20th. day of imipramine administration; she developed a confusional state followed by general epileptiform activity and hyperpyrexia. Autopsy revealed that death was due to pneumonia and though the level of imipramine in the liver was unusually high, the pathologist stated that it was not possible to implicate imipramine directly in leading to death.

NURSING PROBLEMS.

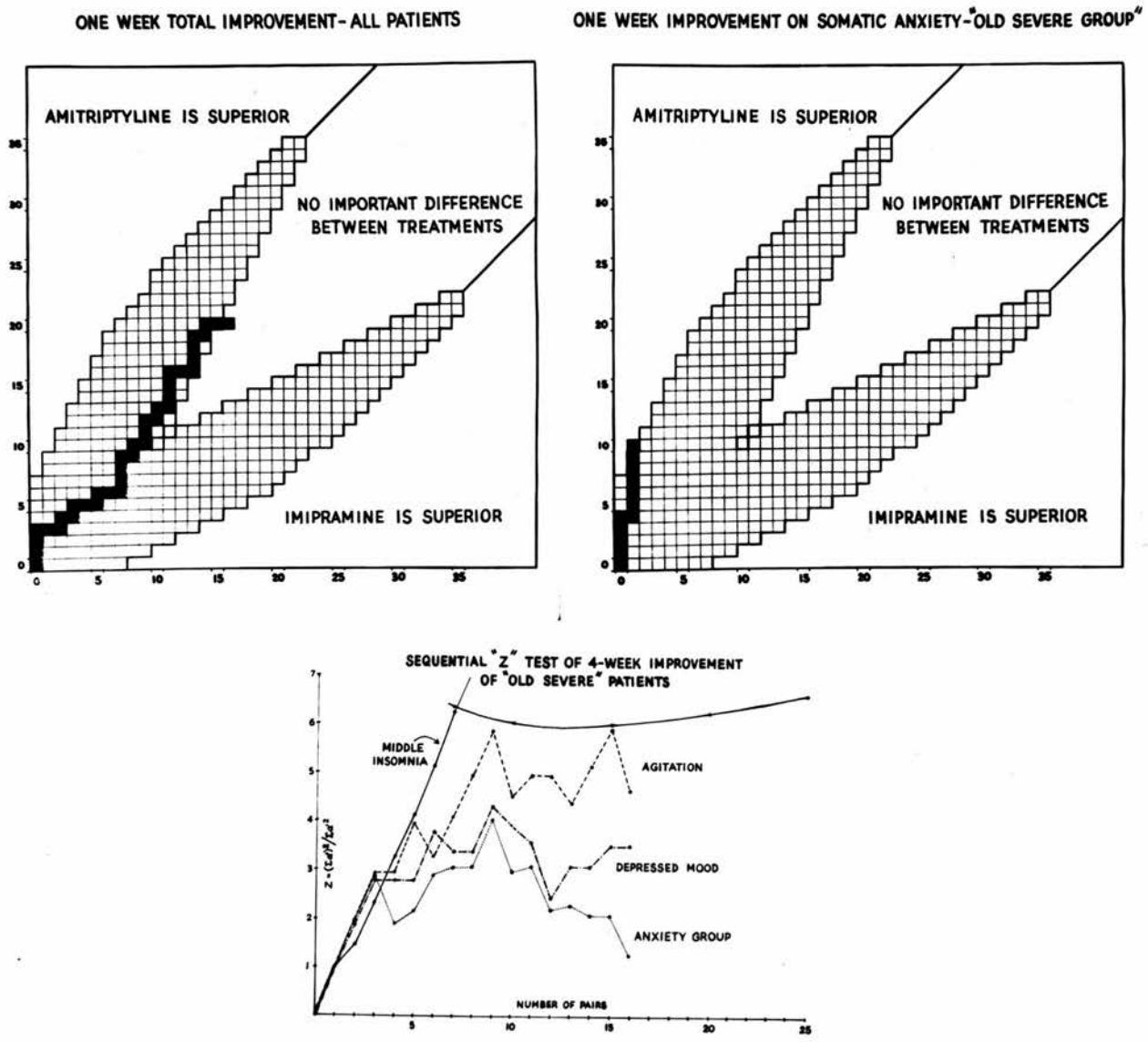
Contrary to expectation, the ease with which the selected patients, many of them severely depressed, were managed during the trial was quite striking. Only one patient was rejected on the grounds of severity (and this because of refusal to take oral medication); none of those accepted had to discontinue the trial in the first four weeks to receive ECT. A few patients required occasional intramuscular injections of chlorpromazine in the early stages of treatment, but this was given

sparingly and only for extreme agitation and distress. This was the more impressive since the great majority of patients spent virtually their entire hospital period in occupational therapy and an adequately, but not specially, staffed open ward.

ANALYSIS OF DATA.

Initially, sequential techniques were used to monitor changes in total scale scores as well as in individual depressive symptoms. Three diagrams illustrating this approach are shown in figure 3.

FIGURE 3.



The top left-hand diagram shows the results of applying a conventional charting procedure to the changes in the total depressive scale scores after one week in 34 pairs of patients: no differences between the drugs are evident. On the other hand, as the right-hand diagram shows, when a more homogenous sample of patients - the "old severes" - was chosen, and a single symptom "somatic anxiety" was selected, the one-week improvement in patients treated with amitriptyline was significantly greater than the improvement occurring in patients treated with imipramine. Next, for greater sensitivity, a more powerful statistical technique was employed - the sequential Z test (Armitage 1960). The lower diagram in figure 3 is a chart of the sequential Z values of the improvement scores in a number of symptoms after four weeks in the "old severe" patients. In the graph, penetration of the "ceiling" denotes statistical significance, an accomplishment rapidly achieved by amitriptyline for "middle insomnia".

Sequential techniques were valuable in pointing up trends and providing a guide to the number of cases needed to produce a significant therapeutic result. In the later analysis, the Mann-Whitney U test, corrected for ties (Siegel 1956), was used to test the significance of differences found between the drug groups on physician's ratings, overall clinical assessments and ratings by occupational therapists. The distribution of these various ratings were rarely normal in appearance and "t" tests or other statistics based on the normal distribution would have been of dubious merit. The probabilities that are quoted in the remainder of the chapter are based on one-tailed tests since the research hypothesis underlying the study specified the direction of the predicted differences between the two drugs.

RATING SCALE SCORES.

Table 5 summarizes the results of the trial in the group of 73 patients in terms of the ability of amitriptyline and imipramine to mitigate the symptoms of depression itemized in Hamilton's scale.

TABLE 5.

MEAN IMPROVEMENT SCORES ON PHYSICIANS' SCALE RATINGS (n=73)

SPECIFIC DEPRESSIVE SYMPTOM	POSSIBLE RANGE OF SCORES	After 1 week		After 4 weeks	
		AMITRIP. (n = 37)	IMIP. (n = 36)	AMITRIP. (n = 37)	IMIP. (n = 36)
Depressed Mood	0 - 8	1 . 4	1 . 2	3 . 2	2 . 4
Retardation	0 - 8	. 7	. 7	2 . 0	1 . 7
Work & Interests	0 - 8	1 . 9	1 . 8	3 . 6	2 . 9
Guilt	0 - 8	. 8	. 8	2 . 1	1 . 5
Suicide	0 - 8	2 . 1	2 . 1	2 . 9	2 . 5
Psychic Anxiety	0 - 8	1 . 6	1 . 6	2 . 8	2 . 4
Somatic Anxiety	0 - 8	1 . 8	1 . 1	1 . 9	2 . 0
Hypochondriasis	0 - 8	. 7	1 . 0	1 . 4	1 . 1
Agitation	0 - 4	1 . 2	1 . 2	1 . 7*	1 . 2
Initial Insomnia	0 - 4	1 . 1	. 8	2 . 2*	1 . 7
Middle Insomnia	0 - 4	. 7*	- . 1	1 . 3	. 8
Delayed Insomnia	0 - 4	. 9*	- . 3	1 . 6*	. 7
Somatic Symptoms (Gastro-Int.)	0 - 4	1 . 2	. 9	2 . 4**	1 . 5
Somatic Symptoms (General)	0 - 4	. 8	1 . 0	1 . 8	1 . 5
Genital Symptoms	0 - 4	. 9	. 7	1 . 6*	. 9
Loss of Weight	0 - 4	. 0	. 0	1 . 9	1 . 6
Loss of Insight	0 - 4	. 3	. 1	. 7	. 3
Total Improvement Score	0 - 100	17 . 9	14. 7	35. 2*	26 . 7

(* Significant at 5% level; ** significant at 1% level)

The table shows that, at the end of one week, amitriptyline tended to be slightly superior to imipramine in alleviating the symptoms of depression. In two symptoms - middle insomnia ($p = .01$) and initial insomnia ($p = .05$) - this superiority was statistically significant. The total improvement score of the amitriptyline group at the end of one week was a little higher than that of the imipramine group, but not significantly so. At the end of one month, however, the superiority of amitriptyline was more in evidence. It was significantly superior to imipramine in relieving gastrointestinal somatic symptoms ($p = .005$), delayed insomnia ($p = .015$), agitation ($p = .04$), initial insomnia ($p = .05$) and genital symptoms ($p = .05$). The total improvement score with amitriptyline was clearly and significantly higher than that produced by imipramine ($p = .02$).

Inspection of the results obtained in the four sub-groups revealed that the drug differences shown by the total group were accompanied by a number of differences in the sub-groups. These differences are shown in table 6, from which the 10 "old mild" and the 4 "young mild" patients have been omitted, since their numbers were too small to allow of valid conclusions. In table 6, all differences with any reasonable possibility of significance are shown. Although the results for the "young severe" and the "old severe" groups are somewhat antithetical, it will be noticed that the picture with regard to insomnia is very consistent - all results favoured amitriptyline, and out of 18 differences, seven were significant ($p < .05$), three of them highly so.

TABLE 6.

SIGNIFICANCE TESTS ON PHYSICIAN'S RATINGS (n = 73)

(All probabilities are associated with the superiority of amitriptyline except those shown in brackets).

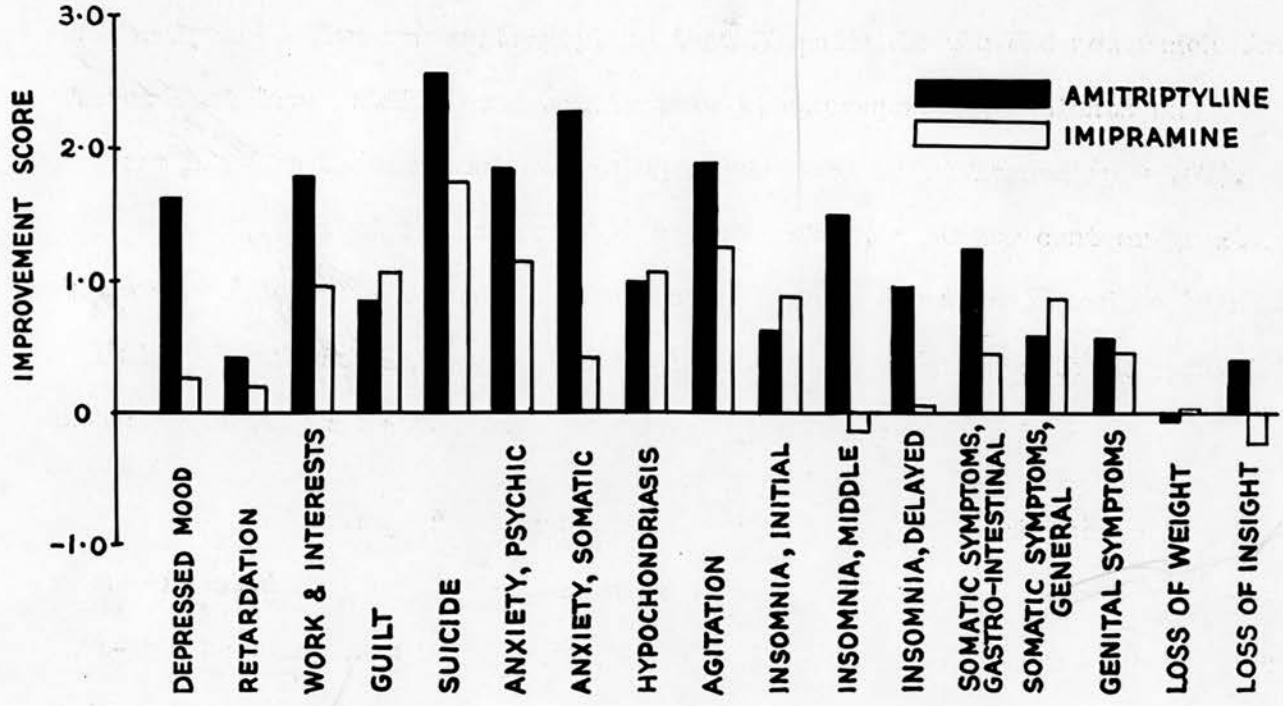
CATEGORY OF PATIENT / SYMPTOM	After 1 week			After 4 weeks		
	"OLD SEVERE" (n = 35)	"YOUNG SEVERE" (n = 24)	TOTAL GROUP (n = 73)	"OLD SEVERE" (n = 35)	"YOUNG SEVERE" (n = 24)	TOTAL GROUP (n = 73)
Dep. Mood	.007**	(.06)		.05*		.06*
Retardation	.14				.16	
Work & Interests	.06	(.06)		.18		.11
Guilt					.11	
Suicide	.09	(.09)		.12	(.23)	
Psychic Anxiety	.14	(.10)		.11	(.26)	
Somatic Anxiety	.008**	(.28)	.13			
Hypochondriasis		(.02)*			(.13)	
Agitation	.14	(.25)		.008**		.04*
Initial Insomnia		.16				.05*
Middle Insomnia	.008**		.05*	.02*		.08
Delayed Insomnia	.09	.11	.01**		.01**	.015*
Somatic Sympt.						
- - - - -Gastro-Int.	.09	(.08)		.02*		.005**
- - - - -General				.40		
Genital Symptoms					.12	.05*
Loss of Weight						
Loss of Insight				.40		
TOTAL	.02*	(.08)		.07		.014*

(* Significant at 5% level. ** Significant at 1% level)

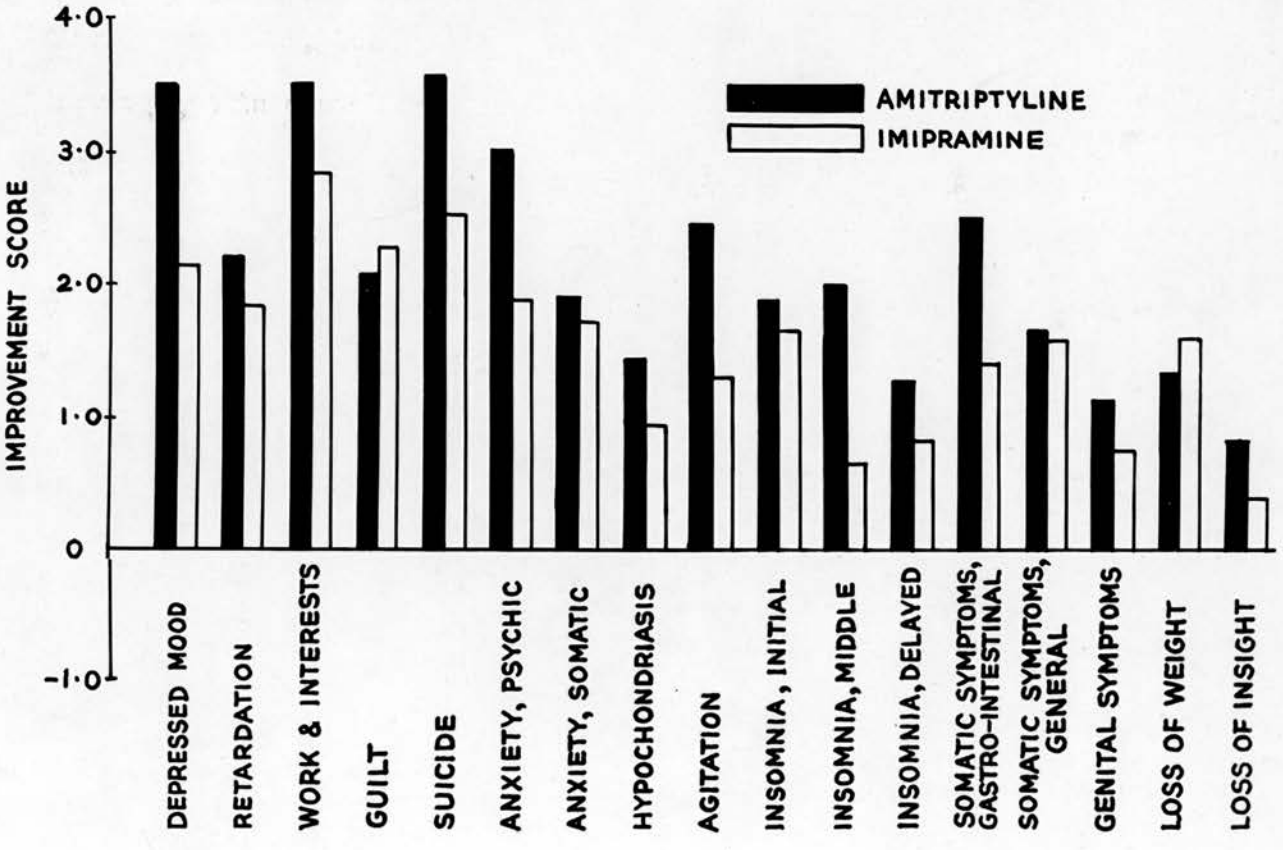
Illustrative diagrams bring out these differences with greater clarity. Figures 4 and 5 show the superiority of amitriptyline in the "old severe" group after one week and one month of treatment.

At the end of one week, amitriptyline was highly significantly superior to imipramine in ameliorating the following symptoms: depressed mood ($p = .007$), somatic anxiety ($p = .008$) and middle insomnia ($p = .008$). The total improvement score of the amitriptyline treated group of patients (19.7) was significantly higher than that of the group on imipramine (9.8, $p = .02$).

MEAN ONE-WEEK IMPROVEMENT – "OLD SEVERE" GROUP (n=35)



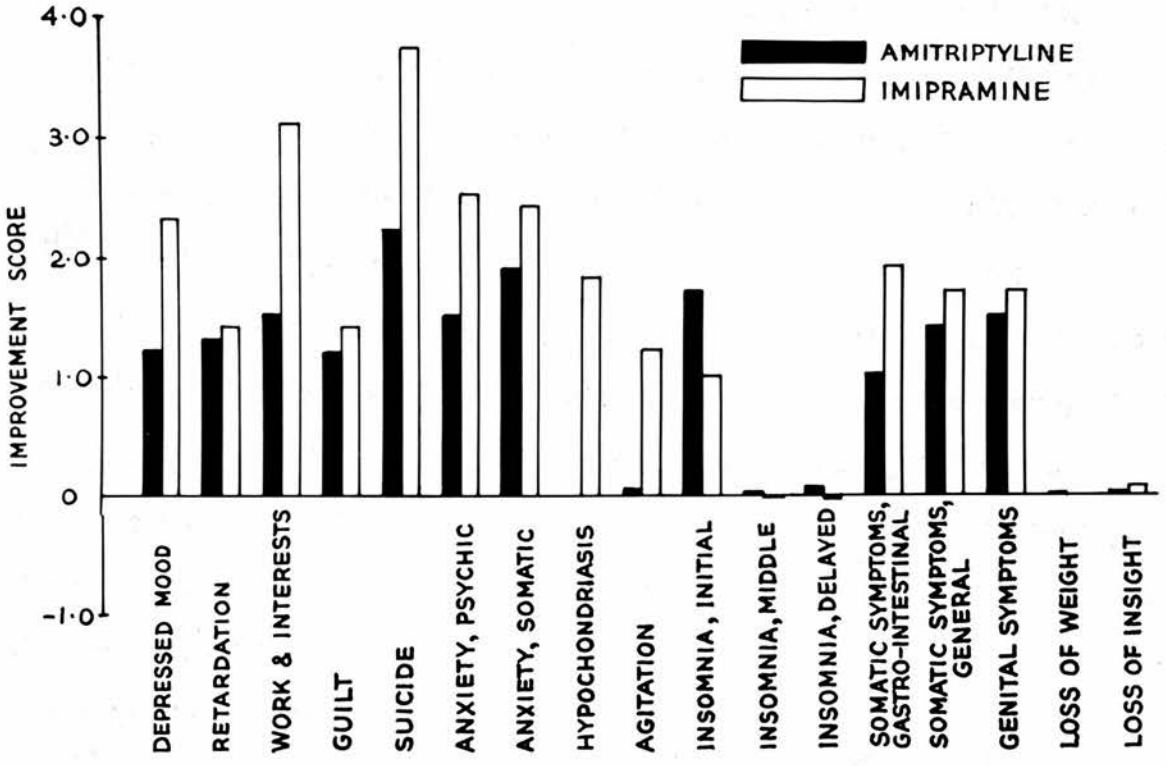
MEAN FOUR-WEEK IMPROVEMENT – "OLD SEVERE" GROUP (n=35)



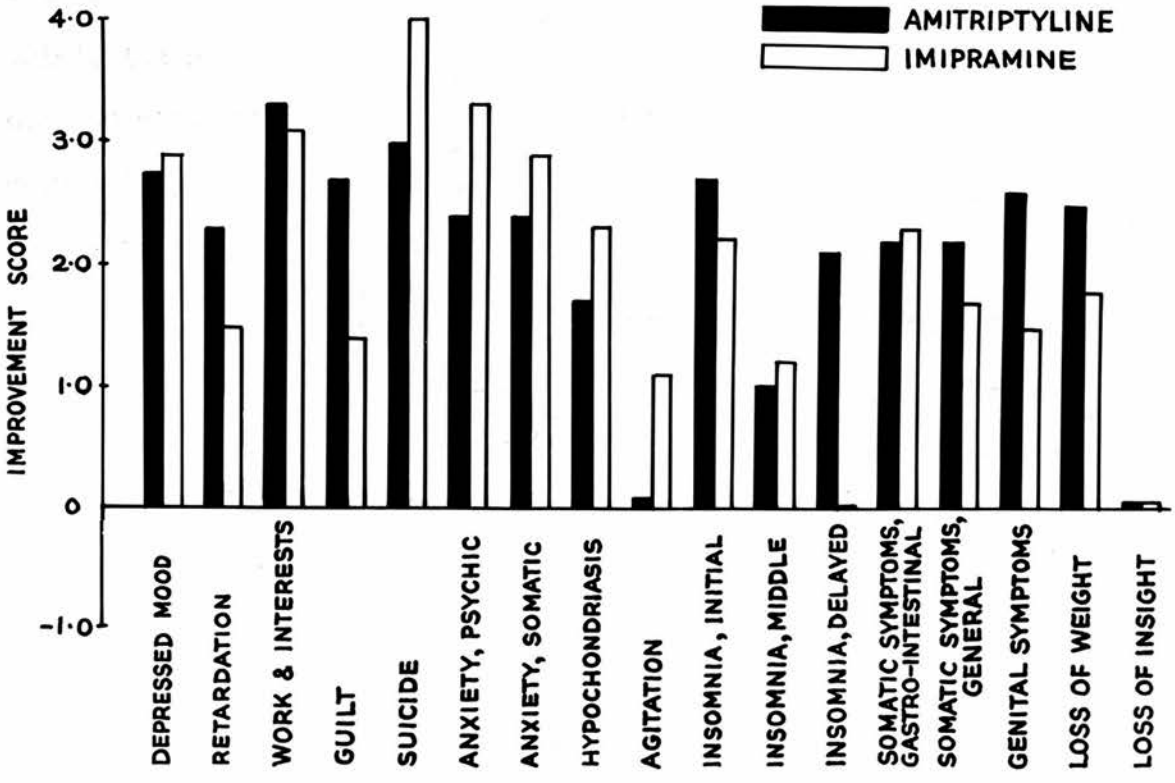
After one month of treatment, amitriptyline was highly significantly superior to imipramine in improving agitation ($p = .008$) and almost as superior in ameliorating gastro-intestinal somatic symptoms ($p = .02$) and middle insomnia ($p = .02$). It was also significantly superior to imipramine in improving depressed mood ($p = .05$). The total improvement score of the amitriptyline treated group (36.3) was not quite significantly higher than that of the imipramine group (26.3, $p = .07$).

Figures 6 and 7 illustrate the rather different picture obtained in the "young severe" patients. After a week, as figure 6 shows, imipramine tended to be better than amitriptyline in relieving symptoms in this type of patient, its superiority attaining significance in hypochondriasis ($p = .02$) and almost reaching it in depressed mood ($p = .06$) and reduction of work and interests ($p = .06$). Gastro-intestinal symptoms were more effectively relieved by imipramine at the end of one week ($p = .08$) and the total improvement score obtained by imipramine at the time (26.3) was also higher than that produced by amitriptyline (19.2, $p = .08$). The various modalities of insomnia were an exception to this general trend. At the end of one month, however, as shown in figure 7, imipramine has lost its pattern of superiority and in no symptom did its superiority reach anywhere near statistical significance. Indeed the total improvement score with imipramine was slightly lower than that achieved by amitriptyline (34.4 versus 37.6). Delayed insomnia in the "young severe" group was highly significantly more effectively relieved by amitriptyline than imipramine.

MEAN ONE-WEEK IMPROVEMENT - "YOUNG SEVERE" GROUP (n=24)



MEAN FOUR-WEEK IMPROVEMENT - "YOUNG SEVERE" GROUP (n=24)



Too few "old mild" patients were available for an adequate comparison of the effects of the two drugs in these types of cases to be made, but suggestive trends could be discerned in the results that were obtained. After one week the five "old mild" patients on amitriptyline showed practically the same improvement in their symptoms as did the five on imipramine. The mean improvement scores of the two groups were very similar (10.6 versus 8.2). After a month amitriptyline was clearly, though not significantly, better than imipramine in relieving depressed mood, reduction of work and interests, hypochondriasis and gastro-intestinal somatic symptoms. By this time the mean total improvement score of the amitriptyline-treated group was appreciably and significantly higher than the group that had received imipramine (27.8 versus 11.0, p = .05).

The two "young mild" depressives who received amitriptyline did better than the two on imipramine both after one week and one month of treatment, but the small size of these groups precluded definite results being obtained.

OVERALL CLINICAL ASSESSMENTS.

The difference between the patients on amitriptyline and on imipramine after one week and one month are shown in the following table.

TABLE 7

MEAN IMPROVEMENT SCORES ON OVERALL CLINICAL ASSESSMENTS (n=73)

CATEGORY OF DEPRESSED PATIENTS	TOTAL GROUP		"OLD SEVERE"		"YOUNG SEVERE"		"OLD MILD"		"YOUNG MILD"	
DRUG	Amit	Imip	Amit	Imip	Amit	Imip	Amit	Imip	Amit	Imip
Number in drug group	n=37	n=36	n=18	n=17	n=12	n=12	n=5	n=5	n=2	n=2
1 week improvement score	1.7	1.3	2.2	1.0	1.5	1.8	1.2	1.6	2.0	0.0
1 month improvement score	3.2	2.4	3.6**	2.3	3.3	2.8	1.8	1.0	3.0	2.0

(** Significant at the 1% level)

The overall ratings for the total group show that, after one week, amitriptyline was more effective than imipramine; after a month this was more evident and almost statistically significant ($p = .06$). The findings were in conformity with the results obtained from the Hamilton scales. In "old severe" patients, the one week improvement on amitriptyline was highly significantly greater than with imipramine ($p = .01$); the trend was still almost significant after a month ($p = .07$). With the exception of the one-week ratings in the two "mild" groups, the direction and amount of change shown by the overall clinical assessments paralleled those shown by the Hamilton scale scores.

OCCUPATIONAL THERAPY RATINGS.

Since some patients included in the trial were not sufficiently well to begin occupational therapy immediately after being put on medication, some O.T. ratings could not be completed until they had been on drugs for several days. Clearly, for these patients, no valid estimate of change on O.T. ratings could be made. Accordingly an arbitrary decision was made not to use ratings completed more than five days after patients had started on drugs; this left 32 sets of ratings suitable for analysis. Nineteen ratings were of patients in the "old severe" group (10 of whom had received amitriptyline) and 13 were on "young severe" cases (6 had been given amitriptyline). As the two groups were so small and as the trends they showed, unlike the physicians' ratings, were similar, these findings were combined to produce the results depicted in table 8.

Higher improvement scores were obtained by patients on amitriptyline on almost all O.T. scale ratings, both after one week and one month of treatment.

TABLE 8.

MEAN IMPROVEMENT SCORES ON OCCUPATIONAL THERAPY RATINGS

BEHAVIOUR IN OCCUPATIONAL THERAPY	POSSIBLE RANGE OF SCORES	AFTER 1 WEEK		AFTER 4 WEEKS	
		Amitrip. (n = 16)	Imip. (n = 16)	Amitrip. (n = 16)	Imip. (n = 16)
Grasp of instructions	0 - 6	.3	-.2	.5	-.4
Attention to task	0 - 6	.8	.3	.2	-.1
Motivation	0 - 6	.4	-.6	.9	-.4
Patient's self-grading	0 - 6	.7	-.4	.8	-.2
TASK PERFORMANCE SUB-TOTAL	0-24	2.2	-.9	2.4	-1.1
Depression	0 - 6	1.0	.6	1.3	.9
Retardation	0 - 6	.7	.1	.9	.7
Agitation	0 - 6	.2	.1	.4	-.6
Physical complaints	0 - 6	.4	.2	.5	.4
SYMPTOM SUB-TOTAL	0 -24	2.3	1.0	3.1	1.4
Rapport with O. T's	0 - 6	.2	.2	.7	1.0
Socialization	0 - 6	.4	.5	1.1	1.0
Overall attitude to O. T.	0 - 6	.1	-.3	.6	-.1
RELATIONSHIPS SUB-TOTAL	0 -18	.7	.4	2.4	1.9
TOTAL	0 -66	5.2*	.5	7.9	2.2

* Significant at the 5 per cent level.

The subtotals and the total scores strongly reflected this trend, though only one difference score, that for the total one-week improvement, was statistically significant ($p = .05$). Nevertheless the one month scores on task performance and depressive symptoms almost attained significance ($p = .07$ and $.06$).

The O.T. scale results were next examined by groups. At the end of one week, the depressive phenomena exhibited in O.T. by the "old-severe" patients were more effectively ameliorated by amitriptyline than by imipramine; the subtotal scores were: task performance 1.8 versus 1.6,

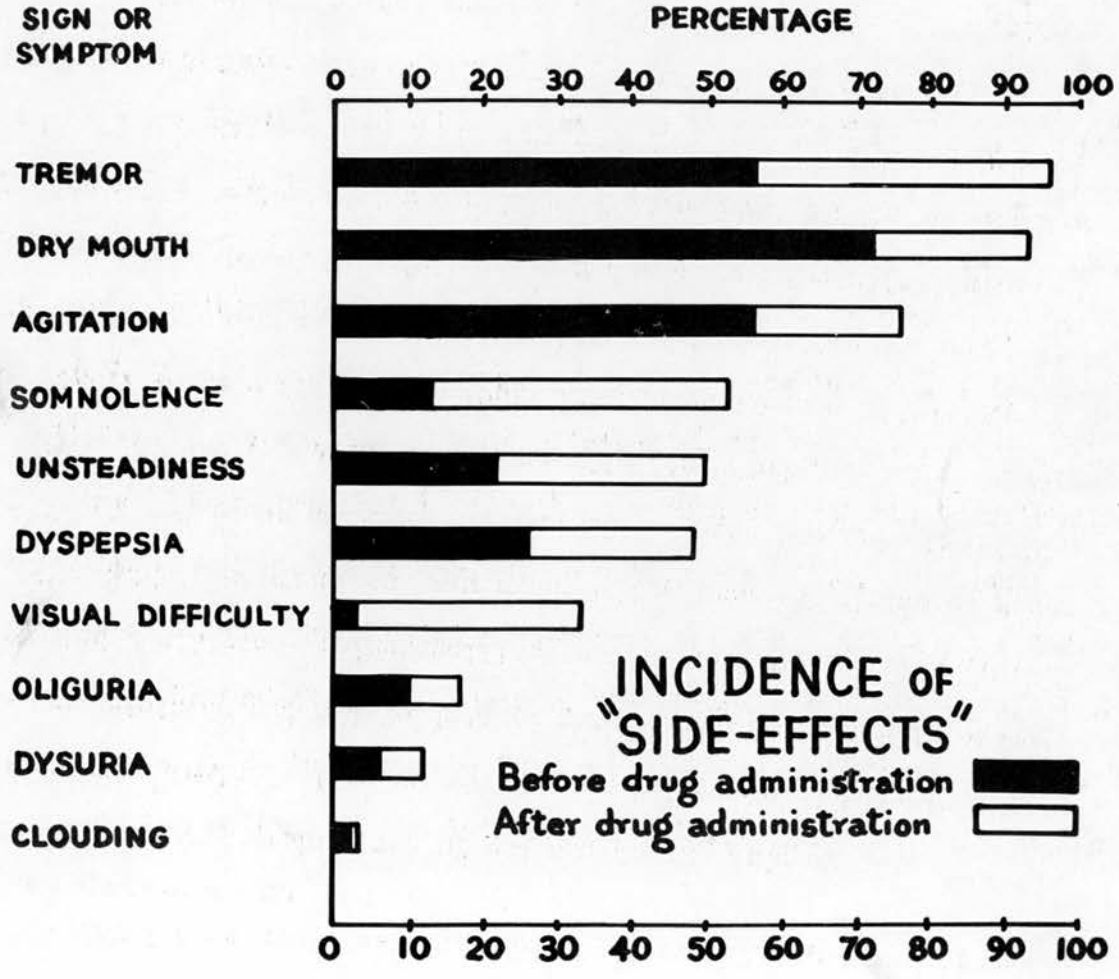
depressive symptoms 2.3 versus 1.0 and relationships 1.6 versus .2; the total scores were 5.7 versus -.1. Nevertheless, none of these differences were statistically significant. After a month, the same trends were maintained, though they still did not reach statistical significance. At this time the task performance scores were 2.3 versus -1.4, the scores for depressive symptoms were 4.3 versus 1.9 and the scores for relationships were 3.7 versus 2.7; the total scores were 10.4 versus 3.2. The "young severe" patients also did better with amitriptyline than with imipramine; the three subtotal scores were 3.2, 2.5 and -.5 for amitriptyline, with a total improvement score of 5.2, versus -.4, 1.0 and .7 for imipramine, with a total improvement score of 1.3. Again the differences did not attain statistical significance. After a month, amitriptyline did better in almost all the items on the scale; subtotal scores were 2.3, 1.2 and 0 for amitriptyline, versus -1.4, 1.0 and 1.0 for imipramine. The total amitriptyline score was 3.5 in contrast to .06 with imipramine, once more a non-significant difference.

RATINGS OF SIDE EFFECTS.

Systematic initial and thrice weekly ratings of side effects were made on 70 patients, 35 on each drug. It was readily possible to classify the twenty groups of side effects on the scale in appendix 3 into ten sub-groups which covered almost all the side effects that were encountered. On this basis, in the dosage that was employed (150 mg. daily for one week followed by 200 mg. daily for a further three or five weeks) both amitriptyline and imipramine appeared to be safe and non-toxic. The side effects of amitriptyline, contrary to expectation, were found to be indistinguishable in severity from those produced by imipramine; and no

significant differences, or even any suggestive trends, were found between the types of side effects produced by the two drugs. With both, side effects were mild and easily tolerated; they diminished or disappeared after three weeks of treatment and were quite unrelated to age. Their incidence before and after drug treatment is shown in figure 8. In examining the diagram however, the reader should note that it depicts only the incidence of side effects, and is no guide to their severity. The high incidence of side effects shown is comprehensible in the light of the fact that each patient was examined 12 (or sometimes 18) times for their presence; even one point (on a four point scale), registered on only one occasion would constitute an addition to the horizontal lines of incidence of which the figure is composed.

FIGURE 8.



With the aid of figure 8, it is possible to divide side effects into three groups, the division being made in terms of the incidence of each side effect before the administration of medication. Group 1 - "visual difficulties" (mainly blurred vision) and "somnolence" - appear to be genuine side effects of both amitriptyline and imipramine. Group 2 - "unsteadiness" (faintness, dizziness and ataxia), "dyspepsia" (heartburn, nausea and vomiting) and "urinary difficulties" (dysuria and oliguria) - seem just as likely to be symptoms of depression as to be drug-induced side effects. The reactions included in Group 3 - "tremor", "dry mouth" and "agitation" - are false side effects - manifestations of depression rather than true side effects of the two drugs.

OUTCOME OF TREATMENT

The following table shows the results obtained in the 73 patients according to the numbers that were discharged with or without electroconvulsive therapy after four and six weeks of drug treatment.

TABLE 9.

OUTCOME OF TREATMENT ACCORDING TO DRUG GROUPS
(n = 73)

	AMITRIPTYLINE (n = 37)	IMIPRAMINE (n = 36)
4 week discharge	22	17
E. C. T.	5	12
6 week discharge	7	4
E. C. T.	3	3
TOTAL discharge	29	21
E. C. T.	8	15

After four weeks, the difference in the number of patients discharged without electroconvulsive therapy on the two drugs very nearly reached statistical significance in favour of amitriptyline ($p = .06$); further a higher proportion of the six week discharges had been on amitriptyline, and the total number of patients discharged on this drug was very nearly significantly higher than the number sent out on imipramine ($p = .06$). In patients who failed to respond to the two drugs the courses of electroconvulsive treatment that were given were administered by physicians other than those involved in the trial. Despite reports to the contrary from other investigators, there was no evidence that fewer treatments than usual were adequate to ameliorate the depressive states of these patients.

To examine the results of drug treatment according to type of depressive illness, the 73 patients were allocated to the endogenous or the reactive categories of depression. The basis for this allocation was (a) family history of affective psychosis, (b) history of previous attack(s) of mania or depression, (c) the presence or absence of appreciable precipitants and (d) the clinical features of the illness. In regard to the latter, no single criterion was regarded as pathognomonic; rather, a constellation of the following features was used in allocating patients to the endogenous category, while reactive cases tended to be diagnosed by exclusion: (1) absence of reactivity to the environment (2) presence of self derogatory trends (3) objectively evident retardation (4) objectively evident agitation (5) presence of delusions and/or hallucinations (6) tendency to symptom-minimization (7) diurnal variation of mood and other functions and (8) terminal insmonia. As might have been anticipated, though 63 patients were fairly easily allocated to one or other category, in 10 the allocation was more difficult; these 10 patients were finally

assigned by "forced choice" into one or other category in terms of preponderance of the criteria that have been enumerated.

Table 10 shows the results that were obtained.

OUTCOME OF TREATMENT ACCORDING TO TYPE OF DEPRESSION

(n = 73)

	ENDOGENOUS (n = 45)		REACTIVE (n = 28)	
	Amitrip.	Imipr.	Amitrip.	Imipr.
Discharge	18*	9	11	12
E. C. T.	7	11	1	4

* Significant at the 5% level.

The superiority of amitriptyline in endogenous cases was statistically significant ($p = .04$). In reactive cases, both drugs achieved good results, amitriptyline again being slightly more effective than imipramine, though not significantly so.

PRELIMINARY CONCLUSIONS REGARDING METHODOLOGY

The allocation of patients into groups according to age and severity proved very useful for, as has been described, different results were obtained in different categories of patients. These differences would have been obscured had analysis been confined to the total group of patients.

In regard to the evaluative techniques that were employed, valuable information was gained. Freyhan, in 1960, pointed out that the effects of antidepressant compounds can, with advantage, be studied in terms

of their ability to ameliorate or abolish specific "target symptoms" of depression; the experiential continuity preserved when drugs are used facilitates assessment of the efficacy of antidepressant therapy. In the present trial Hamilton's scale was found to be very effective in systematically recording the incidence and severity of seventeen common symptoms of depressive states. It took but little time to use and its reliability was attested by an inter-rater agreement, over the first 74 patients, of 0.85; the mean scores of the two raters were 25.72 and 27.01, with standard deviations of 6.9 and 6.4, the difference between the two ratings not reaching statistical significance. The validity of the scale was clear from the fact that in the great majority of cases a drop in the score corresponded with (1) clinical improvement, (2) a drop in the overall clinical assessment and (3) a fall in the occupational therapy rating. In 95 per cent of patients a final score of 10 or less corresponded to discharge. Quite early in the trial Hamilton's scale enabled a number of significant differences to be detected in the effectiveness of the two drugs on specific depressive symptoms, a result that could not have been obtained had reliance been placed entirely on the overall clinical assessments.

The occupational therapy rating scale scores corresponded in general with the Hamilton scale ratings and the overall clinical assessments, though the findings with this instrument in "young severe" patients did not parallel those of the other two. In this connection, there is no evidence that the three instruments were, in fact, measuring the same types of behaviour. The times at which the O.T. ratings were made were not as accurately tied to the schedule of drug administration as were the other two ratings; the occupational therapists had less opportunity to practice with

their scale than the physicians; and the scatter of their scores was very wide. In practice, the occupational therapy scale was simple to use and was rapidly completed; inter-rater agreement was reflected in a correlation coefficient of 0.90. The close conformity of the results that were yielded by this instrument and the Hamilton scale afforded further evidence of the reliability of the general finding in favour of amitriptyline.

SUMMARY OF PRELIMINARY FINDINGS.

According to the various methods of assessment that were used, amitriptyline, in the first 73 patients completing the in-patient phase of the investigation, showed itself to be superior to imipramine in alleviating most of the symptoms of depression. In the total group this superiority, evident though slight after one week, was well marked after one month of drug treatment. The trend was particularly evident in "old severe" patients who, after one week and after one month, exhibited significant improvement both on Hamilton scale scores and on overall clinical assessments. An opposite though barely significant trend was shown by these two instruments in "young severe" patients after one week of treatment; but after a month, amitriptyline paralleled imipramine in therapeutic efficacy. Results in "old mild" and "young mild" patients, too few in numbers for valid comparisons to be made, also tended to suggest that amitriptyline was more effective than imipramine. In regard to symptoms, in relieving insomnia in particular, amitriptyline was more effective than imipramine in every category of patient studied. On the other hand, in regard to side effects, no superiority for amitriptyline could be demonstrated and these symptoms, which occurred equally in both groups of patients, were remarkable only for their paucity and triciality; many, rather than constituting true side effects were manifestations of the depressive syndrome. As judged by outcome of treatment in

terms of discharge or the need for ECT, amitriptyline, which relieved 78 per cent of patients was almost significantly ($p = .06$) superior to imipramine, which relieved 58 per cent. Amitriptyline was significantly superior to imipramine ($p = .04$) in the treatment of endogenously depressed women; both drugs were effective in reactive cases. The majority of these findings have already been reported (Burt, Gordon, Holt and Hordern 1962). Overall the preliminary findings strongly suggested that amitriptyline was a drug of great promise in the treatment of patients with depressive states.

CHAPTER 111.

PHENOMENOLOGY AND PROGNOSTIC VARIABLES

In the second phase of the investigation a further 65 women conforming to the original criteria i.e. female in-patients between 30 and 70 years of age with virtually untreated, relatively "pure" depressive states, were added to the original sample of 74 patients; since two died, the total sample consisted of 137 female patients hospitalized with depressive states. The size of this sample facilitated (1) an investigation of the phenomenology of depressive states in women and (2) a study of the significance of a number of prognostic variables in relation to the drug treatment of depression.

METHODOLOGY OF THE SECOND PHASE

In many ways, the methodology of the second stage of the trial was identical with that employed in the first. The second phase was carried out in the same setting by the same staff; patients were nursed in the same way and, as before, were allocated to groups to receive drugs according to age and the severity of their illnesses. Amitriptyline and imipramine were given in identical capsules in the doses originally laid down i.e. 150 mg. daily for one week, followed by 200 mg. daily for the next three (or five) weeks. After four or, where necessary, six weeks of treatment, definitive decisions on discharge or electroconvulsive treatment were made.

In the interests of efficiency and convenience a number of minor changes were made in the methodology used in the second phase of the investigation. Two additional ratings were obtained:

(1) nurses and physicians (C.G.B. and W.F.G.) together listed the type and content of delusions the patients exhibited.

(2) nurses classified patients into three grades of severity - mild, moderate and severe.

In addition, three procedures employed in the initial phase were discontinued:

(3) those laboratory investigations which were considered superfluous, having shown no change in the first 73 patients, were stopped; these included the haematological examinations (haemoglobin, white blood cell count and the erythrocyte sedimentation rate) and the liver function tests (alkaline phosphatase and cephalin flocculation); estimations of serum bromide level, the Kline reaction and urinalysis were retained.

(4) Occupational therapy ratings were discontinued. As mentioned earlier, many of these ratings, unavoidably made some days after the patients had started their medications, had had to be omitted from the analysis; further, the arrangements necessary to facilitate the ratings proved difficult to sustain in the occupational therapy department.

(5) Ratings of side effects were stopped. These were very time-consuming and, since side effects for the most part were rare and of trivial severity, only customary medical surveillance was maintained.

RESULTS IN THE TOTAL SAMPLE.

The findings in the additional 64 patients corresponded closely with those obtained in the first 73, lending support to the original conclusions. The overall results in the total sample are shown in table 11.

TABLE 11.

OUTCOME OF TREATMENT IN 137 HOSPITALIZED DEPRESSED WOMEN ACCORDING TO DRUG GROUPS

	AMITRIPTYLINE (n = 69)	IMIPRAMINE (n = 68)
4 week discharge	39 (56%)	30 (44%)
E. C. T.	8	23
6 week discharge	17 (25%)	7 (10%)
E. C. T.	5	8
Overall discharge	56** (81%)	37 (54%)
E. C. T.	13	31

**p = .002

The distribution of 137 patients completing the in-patient phase of the trial in terms of age, severity of illness, menopausal state and type of depression, is shown in table 12.

Experience during the trial showed that severe depressives almost invariably had Hamilton scores in excess of 50 rather than 40, the original borderline between mild and severe degrees of depression. Accordingly patients completing the trial were divided into "clinically-mild" depressives (with scores below 50) and "clinically severe" depressives (with scores of 50+).

TABLE 12.

CATEGORIES OF DEPRESSIVES COMPLETING THE IN-PATIENT PHASE OF THE TRIAL (n = 137)
BY AGE AND SEVERITY

SEVERITY	RATING SCALE SCORE	"YOUNG" (30 - 49)		"MIDDLE-AGED" (50 - 59)		"ELDERLY" (60 - 70)	
		Amit.	Imip.	Amit.	Imip.	Amit.	Imip.
"CLINICALLY--MILD" CASES	0 - 39	4	4	8	7	6	6
	40 - 49	7	7	7	5	5	6
"CLINICALLY--SEVERE" CASES	50 - 59	7	10	5	5	5	3
	60+	4	2	8	5	3	8

BY AGE AND TYPE OF DEPRESSION

	Amit.	Imip.	Amit.	Imip.	Amit.	Imip.
ENDOGENOUS (n = 80)	9	7	19	13	14	18
REACTIVE (n = 57)	13	16	9	9	5	5

BY MENOPAUSAL STATE

	PREMENOPAUSAL	MENOPAUSAL	POSTMENOPAUSAL
AMITRIPTYLINE (n = 69)	16	8	45
IMIPRAMINE (n = 68)	10	8	50

Further, an inspection of table 12 reveals that sufficient patients were available to separate the "old" patients (aged 50 - 70) into "middle aged" (aged 50 - 59) and "elderly" (aged 60 - 70) sub-groups. In this way the patients in each drug group were divided into six very comparable sub-groups in place of the four which were originally planned.

Although the patients included in the trial were assigned to homogeneous sub-groups, the criteria for their selection were rigidly adhered to; even so, a number of patients originally included had to be rejected

either during the in-patient phase or shortly afterwards. Two patients died in hospital and two developed retention of urine; these cases will be discussed under "side effects". Apart from these four patients, three schizophrenics, inadvertently admitted to the trial, were omitted from the analysis of the in-patient sample; two patients with personality disorders, one of whom was an alcoholic, were also left out. Finally, two patients, both on imipramine, refused to remain in hospital sufficiently long for their ratings to be completed. The final sample, which took almost a year to collect in a psychiatric hospital currently admitting some 1,500 female patients annually, is thought to be fairly homogeneous. In not more than ten cases was there any doubt as to the primarily affective basis of the syndrome, and in the ten cases which might be regarded as dubious, because of an inadequate personality, alcoholism or a schizophrenic admixture, depression dominated the clinical picture. These cases, like all others, were randomly distributed between the two drug groups.

SIDE EFFECTS.

Side effects were more numerous during the second phase of the trial than they had been in the first. One 69 year-old hypertensive patient, known to be a poor cardiovascular risk, died in her sleep after four days of imipramine medication; it was not felt that death could be attributed to the drug and an autopsy was not performed. Apart from this, medication had to be discontinued in two patients because of retention of urine; one case occurred on each drug, and in both patients the complaint disappeared when the trial capsules were discontinued. The patient who had been receiving amitriptyline was inadvertently put back on this compound by a physician who was unaware she had been in the trial; her retention immediately recurred.

One 56 year-old patient whose depressive state was relieved by amitriptyline developed an acute glaucoma the day after her discharge from hospital; this necessitated an immediate operation. She had exhibited no prior evidence of this disorder, though headache was amongst her depressive complaints. Other side effects, as in the first 73 patients, were mild and of little consequence.

CHARACTERISTICS OF THE TOTAL SAMPLE

SOCIO-ECONOMIC BACKGROUND.

As was to be expected from the method of allocation to the drugs, in socio-economic background there were no significant differences between the two drug groups, and only in very minor ways did the total sample differ from the first 73 patients. Eighty-eight per cent of the patients had been born in Australia and seven per cent were British. The mean age was 52.87 with a standard deviation of 10.02 years. Eighty-eight per cent were, or had been, married and most had two or three children. The great majority had finished their schooling at the primary level or just beyond it, and their vocational qualifications were restricted to semi-skilled, industrial and clerical work. Most were housewives; all the fifteen per cent who worked were employees. Approximately half were dependent on their husband's income, whilst a third subsisted on pensions. Sixty per cent occupied dwellings they owned or were purchasing; the remainder lived in rented houses or flats. The general picture, as in the first 73 patients, was of a predominantly lower-middle-class socio economic-group, with an assured but low income, and low levels of education, vocational training and experience.

PSYCHIATRIC BACKGROUND.

Here too there was no significant difference between the two drug groups and the picture very closely resembled that of the first 73 patients. Forty-eight per cent had never been previously hospitalized for psychiatric illness, and twenty-five per cent had been in hospital only once before. Sixty-four per cent of the patients had first required attention for their mental condition within the last two years. Ten per cent had received antidepressive therapy (within the specified limits) prior to admission: nine patients had been given drugs, whilst one had had ECT. In seventy-seven per cent the illness had developed within one to eight weeks: in twenty-three per cent it had developed more insidiously. Thirty-four per cent had illnesses apparently precipitated by psychological stresses, whilst in seventeen per cent physical precipitants were recorded, such as the puerperium, hypertension and operations. In forty-nine per cent of patients no precipitants were found.

EFFECT OF AGE AND SEVERITY ON INITIAL SYMPTOMATOLOGY.

The effect of age and severity of illness on the symptoms of depression was studied with the aid of the initial symptom scores of the 137 patients completing the in-patient phase of the trial. Table 13 shows the mean symptom severity scores of four groups of patients classified according to age, together with the mean symptom severity scores of four groups classified according to severity of illness, as denoted by their total scale scores.

TABLE 13

DISTRIBUTION OF INITIAL DEPRESSIVE SCALE* SCORES ACCORDING TO AGE AND SEVERITY IN 137 HOSPITALIZED FEMALE DEPRESSIVES.

	DEPRESSIVE SYMPTOM	RANGE OF SCORES	AGE				SEVERITY			
			30-39 (n=22)	40-49 (n=23)	50-59 (n=50)	60-70 (n=42)	< 40 (n=35)	40-49 (n=37)	50-59 (n=35)	60+ (n=30)
1	Depressed Mood	0-8	4.00	4.65	4.78	5.05	3.63	4.46	4.74	6.27
2	Retardation	0-8	2.77	3.30	3.24	3.21	2.17	3.11	3.14	4.43
3	Work and Interests ↓	0-8	4.82	5.30	5.24	5.31	4.03	5.05	5.46	6.47
4	Guilt	0-8	2.77	2.70	3.00	2.76	.94	2.03	3.57	5.13
5	Suicidal proclivities	0-8	3.32	3.43	3.90	2.95	1.51	3.22	4.03	5.27
6	Anxiety, psychic	0-8	5.32	4.78	4.60	5.12	3.26	4.62	5.57	6.40
7	Anxiety, somatic	0-8	4.36	3.69	3.42	3.55	2.23	3.24	4.11	5.30
8	Hypochondriasis	0-8	2.09	2.17	1.54	1.57	.74	1.46	2.2	2.73
9	Agitation	0-4	1.27	1.74	2.64	2.45	1.14	1.67	2.71	3.43
10	Insomnia, initial	0-4	3.04	3.30	2.88	3.02	2.23	3.03	3.31	3.60
11	Insomnia, middle	0-4	1.77	1.43	1.56	1.81	.86	1.59	1.97	2.27
12	Insomnia, delayed	0-4	1.18	2.26	2.30	2.19	1.43	2.00	2.23	2.77
13	Somatic symptoms, gastrointestinal	0-4	2.82	2.74	2.72	2.88	1.94	2.78	3.06	3.47
14	Somatic symptoms, general	0-4	3.27	3.35	2.84	3.00	2.14	2.84	3.46	3.87
15	Genital symptoms	0-4	3.00	2.17	1.12	0.45	.69	1.51	1.86	1.53
16	Loss of Weight	0-4	1.77	2.70	2.16	2.48	1.80	1.73	2.66	3.17
17	Loss of Insight	0-4	0.82	0.43	0.52	0.86	.09	.41	.71	1.57
	TOTALS:	0-100	48.50	50.16	48.54	48.38	30.57	44.76	54.80	67.83

* HAMILTON, M. (1960) "A Rating Scale for depression " J. Neurol. Neurosurg. and Psychiat. 23:56-62.

AGE.

Five symptoms showed significant alterations in severity according to age, despite the fact that no significant differences existed in the mean total scale scores of any of the four groups (Kolmogorov-Smirnov test). In the "very young", genital symptoms were significantly more severe than in the "elderly" (75% versus 10%, $p < .001$) but in the latter group agitation (61% versus 29%, $p < .05$), delayed insomnia (55% versus 29%, $p < .05$), loss of weight (62% versus 44%, $p < .02$) and depressed mood (63% versus 50%, $p < .06$) were significantly more severe.

SEVERITY OF ILLNESS

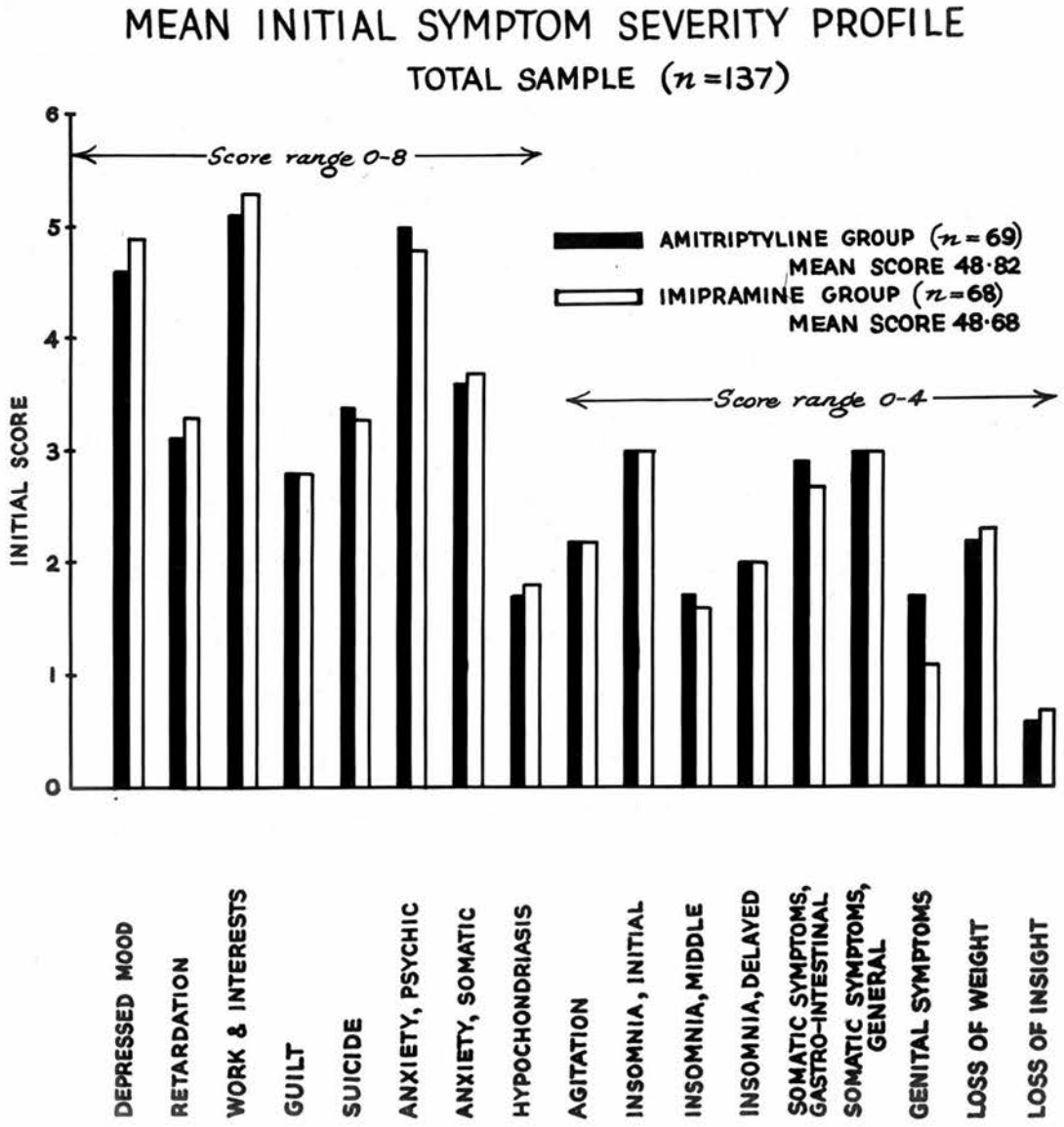
Five symptoms showed a disproportionately greater increase in severity than that registered by the mean total severity score. Whereas the latter score rose from 30.57 to 67.83, approximately doubling itself, the

following symptoms increased more than threefold; agitation (28% rising to 86%, $p < .001$) guilt (12% increasing to 64%, $p < .001$) suicidal proclivities (19% rising to 66%, $p < .001$), loss of insight (0% rising to 39%, $p < .01$) and hypochondriasis (9% increasing to 34%, $p < .05$).

INITIAL SYMPTOM SEVERITY PROFILE

The mean initial symptom severity profile of the 69 patients who received amitriptyline and the 68 who were given imipramine is shown in figure 9. Clearly the two groups were almost identical in respect of initial symptomatology.

FIGURE 9



PROGNOSTIC VARIABLES

A number of variables were examined to investigate their prognostic value in relation to discharge or referral to ECT. The variables were (1) the Hobson scale score (2) the initial severity of the depressive symptoms (3) the presence of delusions (4) the effects of age, menopausal state, type of depression and severity and (5) the response to one week of treatment. The decision as to discharge or ECT was made, it should perhaps again be emphasized, entirely on a "blind" basis i.e. the two physicians making the decision had no idea which drug the patient in question had been receiving. This objective criterion of the success of drug therapy - discharge or ECT - was of great value in assessing the results of the investigation.

THE HOBSON SCALE

In 1953 Hobson published a method for scoring a number of favourable and unfavourable clinical features associated with the outcome of depressives treated with electroconvulsive therapy. Later Roberts (1959), who studied prognostic features with electroshock treatment in 50 female depressives, found a correlation between Hobson score and outcome of .73 interviewing after one month and .67 two months later. On the other hand, Hamilton and White (1960), who examined the outcome of depression treated with ECT in 49 male in-patients, found a correlation with Hobson score of .18, which was not significant. Hamilton and White attributed their lower figure to the fact that their patients were more severely ill than those studied by the other two investigators.

In the present series of patients, scale scores were allocated according to the method advocated by Hobson. At the conclusion of the in-

patient phase of the investigation the Hobson scores of 130 patients were available for examination. The results in the total group, the two drug groups and their twelve sub-groups of patients are shown in table 14.

TABLE 14

HOBSON SCALE SCORES IN 130 HOSPITALIZED FEMALE DEPRESSIVES

CATEGORY OF PATIENT	OUTCOME	AMITRIPTYLINE			IMIPRAMINE		
		Total Score	Number of patients	Mean Score	Total Score	Number of patients	Mean Score
YOUNG CLINICALLY-MILD (Aet 30-49, scale score 0-49)	DISCHARGE	58	10	5.8	32	7	4.6
	E.C.T.	10	1	1.0	15	3	5.0
YOUNG CLINICALLY-SEVERE (Aet 30-49, scale score 50 +)	DISCHARGE	23	6	3.8	28	6	4.7
	E.C.T.	11	4	2.7	19	6	3.2
MIDDLE-AGED CLINICALLY-MILD (Aet 50-59, scale score 0-49)	DISCHARGE	49	13	3.8	24	7	3.4
	E.C.T.	8	2	4.0	22	4	5.5
MIDDLE-AGED CLINICALLY-SEVERE (Aet 50-59, scale score 50 +)	DISCHARGE	34	11	3.1	15	5	3.0
	E.C.T.	5	2	2.5	18	5	3.6
ELDERLY CLINICALLY-MILD (Aet 60-70, scale score 0-49)	DISCHARGE	28	7	4.0	18	6	3.0
	E.C.T.	8	2	4.0	13	4	3.2
ELDERLY CLINICALLY SEVERE (Aet 60-70, scale score 50 +)	DISCHARGE	13	6	2.2	12	2	6.0
	E.C.T.	6	2	3.0	20	9	2.2
TOTAL GROUP	DISCHARGE	205	53	3.9	129	33	3.9
	E.C.T.	48	13	3.7	107	31	3.4

Clearly, the variations in the scale scores are insignificant, whether the total group, the two drug groups or their twelve sub-groups are examined. The total Hobson score was of no value in predicting outcome with either drug, whether the entire group or the six sub-groups were considered. Nor was the situation much better in regard to individual scale items; of sixteen such items, only two - lack of insight and neurotic traits in adult life - showed a significant difference between the two drugs. In the total group, in regard to the presence of both these clinical features, the number of patients discharged without ECT on amitriptyline was significantly higher than the corresponding number discharged on imipramine ($p < .05$ and $< .02$ respectively); the proportions of responders and non-responders merely

reflected the proportions responding to the two drugs. Evidently therefore, with both drugs, absence of insight and the presence of neurotic traits in adult life did not significantly alter the subsequent outcome.

INITIAL SEVERITY OF DEPRESSIVE SYMPTOMS

The initial severity of each of the seventeen symptoms included in Hamilton's scale was examined in relation to the outcome of the patients in the two drug groups. In amitriptyline-treated patients, the severity of their initial symptoms was not of predictive value; but in imipramine-treated patients, on the other hand, marked severity in any of five symptoms was associated with a significantly larger proportion receiving ECT. These symptoms were: reduction of work and interests ($p < .001$), depressed mood ($p < .01$), agitation ($p < .02$), psychic anxiety ($p < .05$) and retardation ($p < .05$). Further, when in order to assess the effect of the two drugs on severe symptoms, the highest scores were examined i.e. scores of five or more for the first eight symptoms and two or more for the last nine, amitriptyline was significantly more effective in twelve of the seventeen symptoms. These were: depressed mood ($p < .001$), reduction of work and interests ($p < .001$), agitation ($p < .01$), middle insomnia ($p < .01$), general somatic symptoms ($p < .01$), loss of weight ($p < .01$), psychic anxiety ($p < .02$), initial insomnia ($p < .02$), retardation ($p < .03$), terminal insomnia ($p < .05$), gastrointestinal somatic symptoms ($p < .05$) and loss of insight ($p < .05$).

DELUSIONS

Friedman, Mowbray and Hamilton (1961), amongst other authors, have pointed out that patients who are frankly deluded do badly on imipramine. In the present series of 137 patients, 27 (20%) had unequivocal delusions; 23 of these, 17 on imipramine and 6 on amitriptyline, were typically and characteristically depressive, whilst in 4 "dubious" cases, all on amitriptyline, a schizophrenic admixture was present. Delusions were commoner in

patients over 50 than in those who were younger (22 versus 7, p = .12: if the 4 "dubious" cases are omitted, p = .06); in addition, delusions were significantly more frequent amongst the clinically-severe cases than amongst the clinically-mild (21 versus 6, p = .02). Twenty-three of the 27 patients who were deluded required ECT, six of the ten who were receiving amitriptyline and all 17 patients on imipramine; two of the four deluded patients who responded to amitriptyline were those allocated to "dubious" category. In regard to outcome of treatment, the 59 non-deluded patients on amitriptyline did highly significantly better than the 10 who were deluded; 56 (88%) were discharged and 7 required ECT in the non-deluded group versus 4 (40%) discharged and 6 requiring ECT in the deluded group ($p < .01$). The same was true for imipramine; of 51 non-deluded patients receiving the drug, 37 (73%) were discharged without ECT in contrast to none discharged without ECT of the 17 that were deluded, a difference that is very highly significant ($p < .001$). It is clear therefore that depressive delusions, which, as might be expected, most frequently occur in older patients and in those with severer degrees of depressive illness, are of bad prognostic import in regard to the drug treatment of depression. In the present investigations this was rather more the case with imipramine than with amitriptyline.

AGE, MENOPAUSAL STATE, TYPE OF DEPRESSION AND SEVERITY

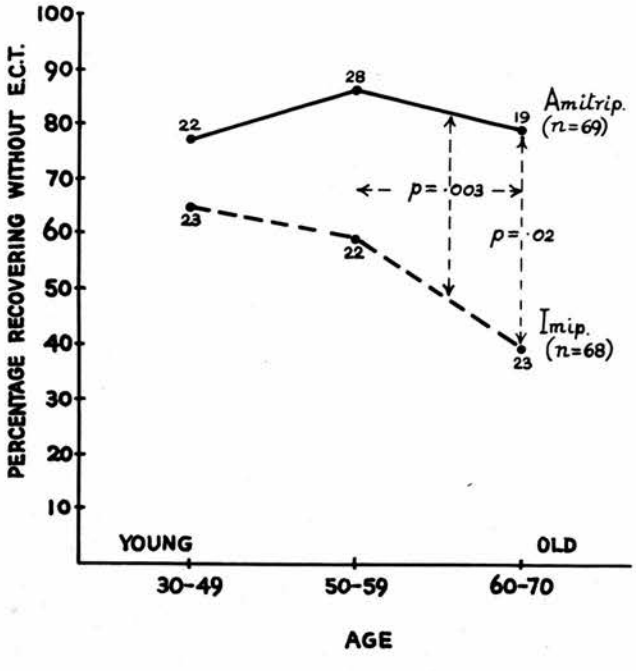
In the following graphs illustrating the effects of these variables, the number of patients in each sub-group is indicated to enable ready perception of instances where large differences are associated with small numbers of patients. Exact probabilities, based on chi-square or Fisher's Exact Test (two tail), are shown for all statistically significant differences. Accordingly, any large differences not indicated to be significant should be interpreted with caution.

AGE AND MENOPAUSAL STATE

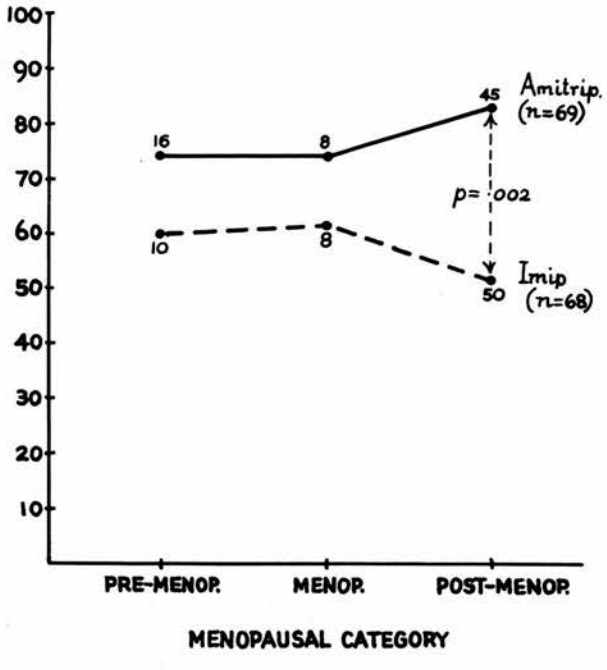
FIGURE 10

OUTCOME ACCORDING TO

(a) AGE



(b) MENOPAUSAL CATEGORY

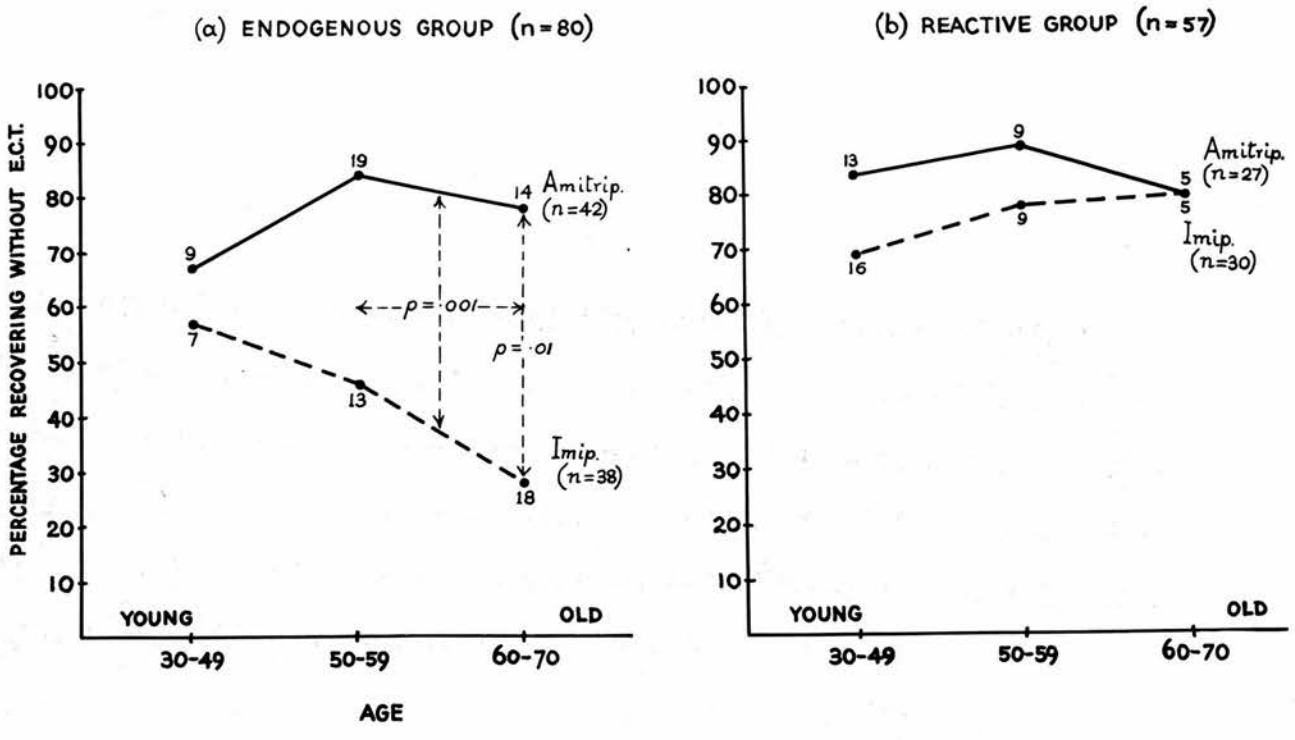


Amitriptyline was superior to imipramine in alleviating the depressive states of the 50 "middle aged" and the 42 "elderly" patients. In the combined "old" group of 92 patients, thissuperiority exceeded the 1 per cent level of significance. A similar trend was evident in the 95 post-menopausal cases (p = .002), though no significant difference could be demonstrated for pre-menopausal and menopausal patients.

TYPE OF DEPRESSION

FIGURE 11

OUTCOME ACCORDING TO TYPE OF DEPRESSION



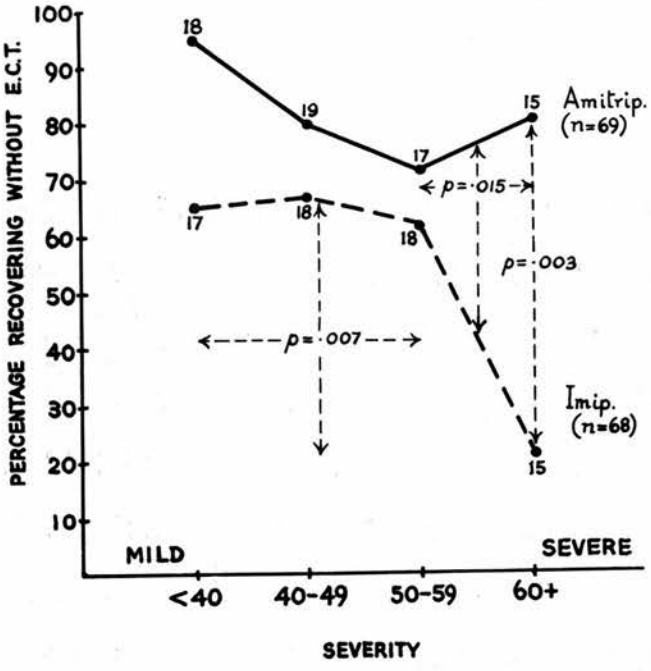
The superiority of amitriptyline over imipramine in patients with both endogenous and reactive types of depression is shown in the two graphs in figure 11, though only in endogenous cases did this superiority attain statistical significance (p = .001). Thus the earlier findings in respect to amitriptyline shown in table 10 (page 79) were confirmed.

SEVERITY OF DEPRESSION

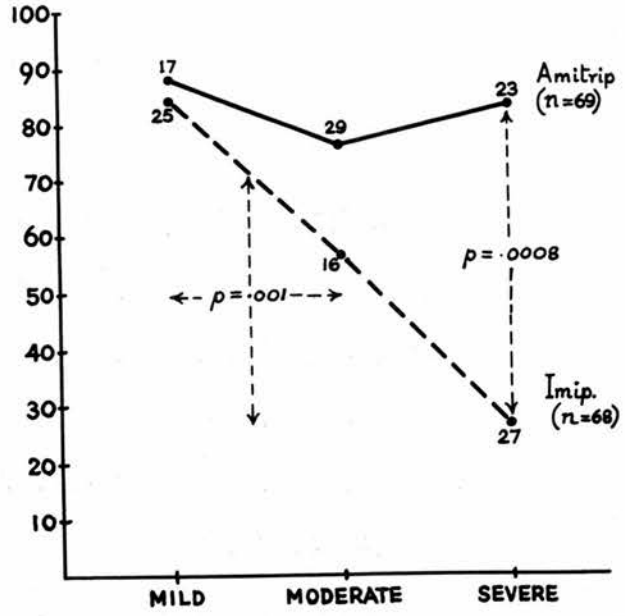
FIGURE 12

OUTCOME ACCORDING TO SEVERITY IN TERMS OF

(a) PHYSICIANS' RATINGS (n = 137)



(b) NURSES' RATINGS (n = 137)



The graph shown in figure 12 (a) demonstrates the effect of severity of illness on the outcome of treatment with the two drugs according to assessments made by the two physicians engaged in rating procedures. Hamilton scale scores were used since overall clinical assessments corresponded closely with them, and since the scores could be precisely analysed in terms of individual symptoms and clusters of symptoms. It is readily evident that whilst patients on amitriptyline did well at all levels of severity, the improvement noted in the severest cases was outstandingly better than that achieved by imipramine ($p = .003$). The very severe (score 60+) cases on imipramine did particularly poorly, only attaining a 20 per cent level of recovery; at this level of severity, imipramine was significantly less

effective than it was in milder cases (p = .007).

Figure 12 (b) shows the effect of severity of illness on the outcome of treatment with the two drugs according to the nursing staff's blind ratings of severity. These were made by three sisters on the basis of the patient's behaviour in the ward during the trial. All patients were assigned to three groups - mild, moderate and severe. The mild group had, the nurses felt, only minimal symptoms, whereas the illnesses of the severe group were characterized, they thought, by "depressive delusions, depressive hallucinations, ideas of hopelessness or guilt, psychomotor retardation or severe agitation, lack of responsiveness and loss of interest in self, people and surroundings." Only 26 (62%) of the 50 patients the nurses regarded as "severe" recovered without ECT; despite this, the graph of their ratings shows that the drug success rate was very high in the amitriptyline group: 19 (83%) out of 23 recovered with amitriptyline, versus 7 (26%) of 27 on imipramine (p = .0008). These figures correspond reasonably closely with those obtained from the physicians' scales (amitriptyline 80% success according to physicians, 83% according to nurses; imipramine 20% according to physicians, 26% according to nurses). Like the physicians' ratings, the nurses' ratings showed that, in severely depressed patients, imipramine was much less effective than it was in milder cases (p = .001).

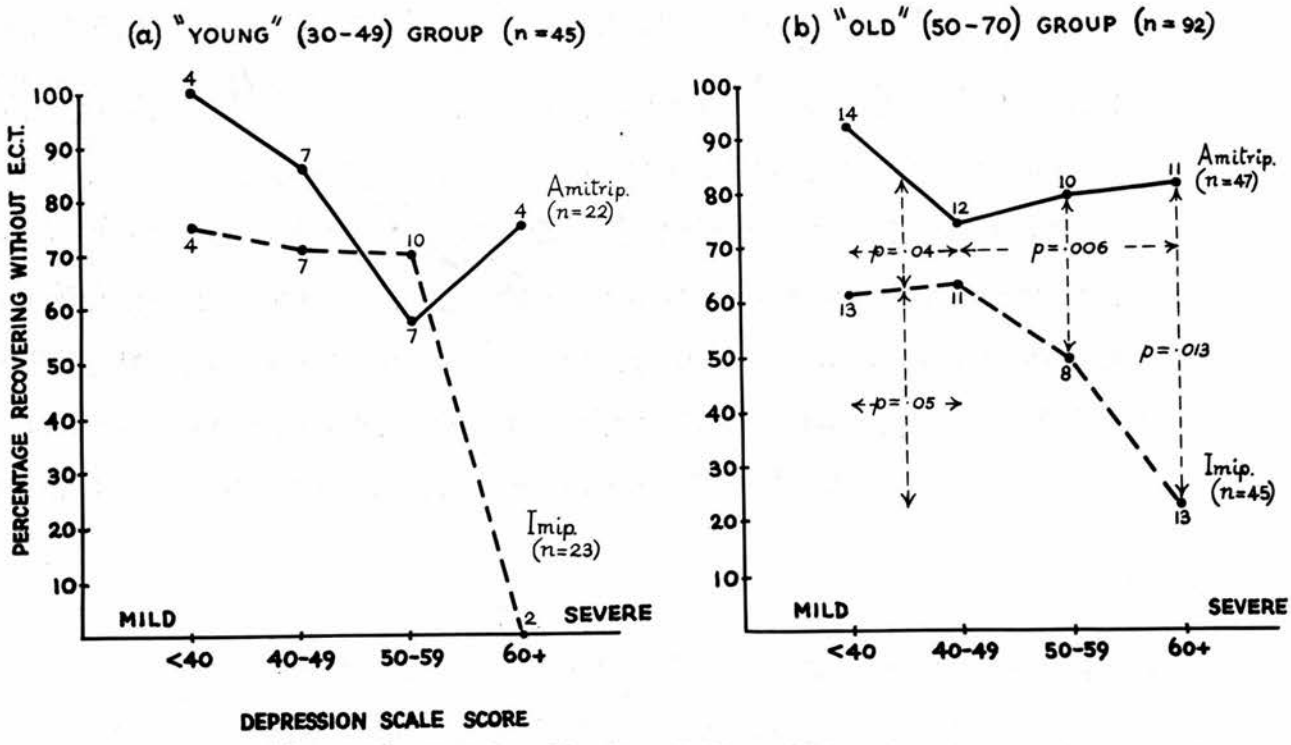
The higher effectiveness of amitriptyline in very severe depressives may have been related to the group containing a lower proportion of unequivocally depressively deluded patients than the corresponding group on imipramine. Of fifteen patients with Hamilton scores of 60 or more treated with amitriptyline, four had unequivocal depressive delusions; among fifteen corresponding patients receiving imipramine, nine were similarly deluded.

COMBINED EFFECT OF AGE AND SEVERITY

It was thought possible that there was a relationship between age and severity as factors in the eventual outcome. To demonstrate this, the percentage recovering with each drug, according to severity in "young" and "old" patients, was graphed.

FIGURE 13

OUTCOME ACCORDING TO AGE AND SEVERITY OF ILLNESS



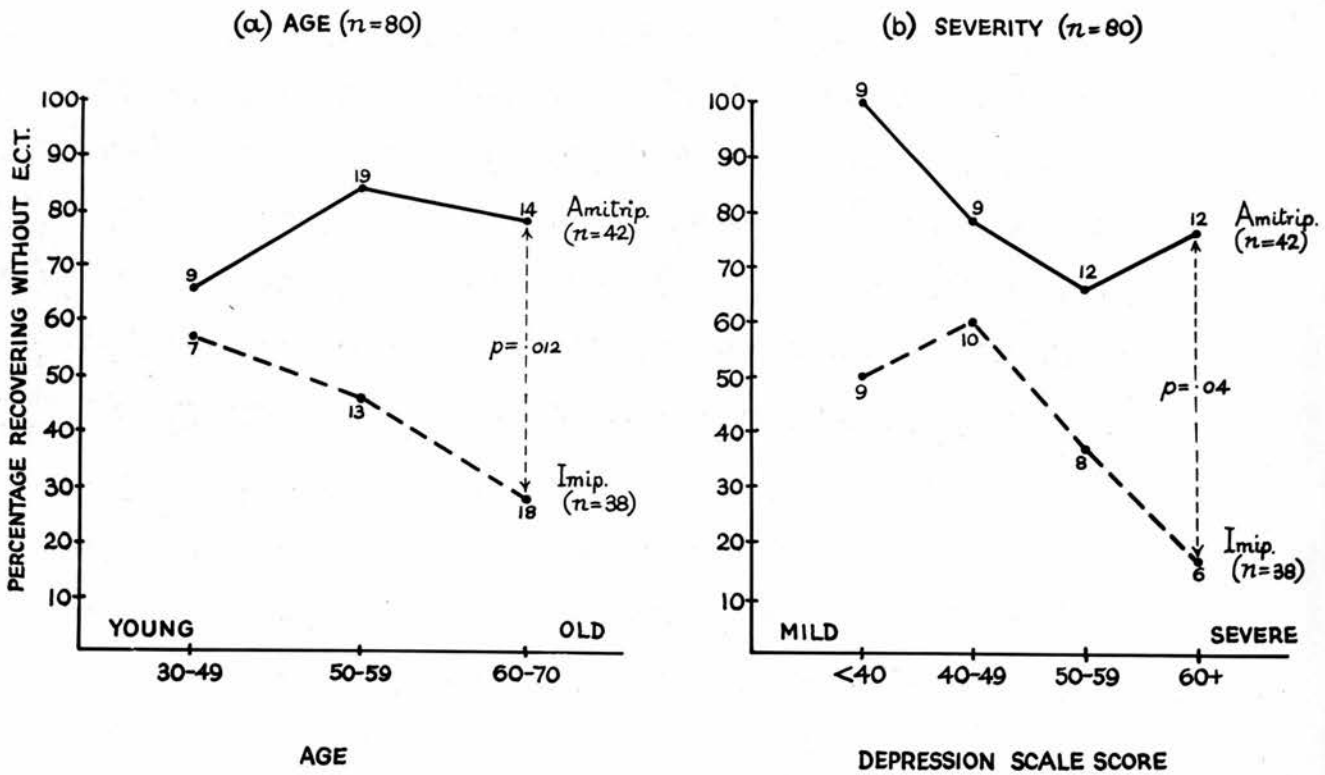
The numbers of patients at the mild and severe extremes of the "young" group were too small to allow of valid conclusions, but it is interesting to note that the trend they exhibited paralleled that shown by the corresponding extremes of the "old" group. Age would therefore seem to have had rather less effect in influencing outcome than severity of illness. In the "old" group, amitriptyline was significantly superior to

imipramine in both clinically-mild (p = .04) and clinically-severe cases (p = .006). Imipramine was significantly less effective in clinically-severe "old" depressives than it was in clinically-mild cases in the same age group (p = .05).

EFFECT OF AGE AND SEVERITY IN ENDOGENOUS CASES

FIGURE 14

OUTCOME IN ENDOGENOUS CASES ACCORDING TO



The graphs demonstrate that amitriptyline was superior to imipramine in endogenous depression at all ages and at all levels of severity. As age increased, the efficacy of amitriptyline tended to rise, whereas that of imipramine fell off; the latter compound was significantly less effective than amitriptyline in elderly patients (p = .01) and in very severe cases (p = .04). With increasing severity, there was some decline in the effective-

ness of amitriptyline, though among the 24 clinically-severe patients who received this drug, the rate of successful response still reached the high level of 71 per cent. Imipramine by contrast fell off dramatically in effectiveness with increasing severity: thus amongst the 20 clinically-severe patients who received imipramine, the average response rate was only 27 per cent.

RELATIONSHIP BETWEEN MAJOR VARIABLES

It seemed probable that a relationship existed between age, menopausal category type of depression and severity of illness. Accordingly, correlation coefficients were computed for these four variables. Each was dichotomized as follows: (1) age - "young" (30 - 49) versus "old" (50 - 70); (2) menopausal category - premenopausal and menopausal versus postmenopausal; (3) type of depressive illness - reactive versus endogenous and (4) severity of illness - clinically-mild versus clinically-severe. The inter-correlations are shown in table 15, the correlations being computed by means of the phi-coefficient (phi = $\sqrt{\text{chi-square} / N}$).

As might be expected, table 15 reveals that a close relationship existed between age, menopausal category and type of depression. "Young" patients were usually pre-menopausal or menopausal and tended to suffer from reactive depressions; "old" patients were usually postmenopausal and frequently suffered from endogenous depressive states. On the other hand a weaker relationship existed between these variables and severity of illness. Significant, though low, intercorrelations were found between type of depression and menopausal category on the one hand and severity on the other; but no correlation was found between age and severity. It appears therefore that age and severity of depression can be taken as independent prognostic criteria.

TABLE 15.

RELATIONSHIP BETWEEN FOUR MAJOR VARIABLES IN 137 HOSPITALIZED FEMALE DEPRESSIVES

	AGE	MENOPAUSAL CATEGORY	TYPE OF DEPRESSION	SEVERITY
AGE		.63***	.31***	.02
MENOPAUSAL CATEGORY			.42***	.17*
TYPE OF DEPRESSION				.18*
SEVERITY				

*** : Significant at the 0.1 per cent level.

** : Significant at the 1 per cent level.

* : Significant at the 5 per cent level.

An analysis of variance of "improvement" scores of 120 patients was carried out in order to explore further the relationship between drugs, age and severity as predictors of improvement. With two drugs, three age-groups and four levels of severity, the patients were grouped into 24 cells for the analysis of variance. Where a cell contained more than five patients, one or more were randomly withdrawn, and six cells had to be built up to the required number by the addition of the most nearly matching patients from an adjacent cell.

The reduction of the group to 120 left virtually unchanged the percentage of patients discharged and receiving ECT (new sample: amitriptyline discharged 80%, imipramine discharged 52% - total group: amitriptyline

discharged 81%, imipramine discharged 54%).

For the analysis of variance, scores were computed from patients percentage improvement in scores on the Hamilton scale by the final ratings (after four to six weeks). These percentages were transformed to a normalized distribution with mean = 0 and standard deviation = 1.

TABLE 16

ANALYSIS OF VARIANCE

SOURCE	d, f	S S	Mean. Sq.	F with combined error term as denominator
a) Drugs	1	6.166	6.166	7.05 ($p < .01$)
b) Severity	3	3.744	1.248	
c) Age	2	.610	.305	
d) Drugs x Severity	3	8.902	2.967	3.39 ($p < .05$)
e) Drugs x Age	2	.396	.198	
f) Severity x Age	6	5.763	.961	
g) D x S x A.	6	6.170	1.028	
h) Within groups	96	83.948	.874	
TOTAL	119	115.699		
Combined e, f, g, h.	110	96.277	.875	

The results of the analysis are shown in table 16. The difference between the mean for drugs was highly significant and the drug x severity interaction was significant at the 5 per cent level of confidence. Analysis of variance for the two drug-severity columns separately indicated no significant F for the amitriptyline group and an almost significant F for the imipramine group. The differences within the imipramine group were tested by means of the t - test and it was found that the mean improvement score for the "moderate" group was significantly ($p < .05$) higher than those for the mild and the very severe groups.

An examination of the comparability of this new "improvement" score and the criterion of "outcome" usually employed in the study showed the two to be very highly correlated. Phi-correlations for the two criteria were: .85 for the whole sample, .76 for the amitriptyline group and .88 for the imipramine group.

RESPONSE AFTER ONE WEEK OF TREATMENT.

As has already been mentioned in the patients under investigation amitriptyline produced an 81 per cent rate of recovery without ECT in contrast to a rate of 54 per cent achieved by imipramine. To what extent was this improvement foreshadowed by the degree of improvement after one week of treatment? The improvement evident at this time was in some degree undoubtedly due to "milieu effect" for, of the 137 patients included in the investigation, 92 (67%) after a maximum period of one day in the (locked) admission ward, were moved into an open convalescent ward. The lack of a group of patients on placebo made it impossible to assess the degree of improvement due to this factor, but the design of the trial enabled "milieu effect" to be discounted as a between-drug variable for all patients were equally exposed to it and no significant difference existed between the periods the patients on the two drugs spent in the admission ward.

Although only two significant differences between drugs were evident when the first-week symptom improvement scores of the total sample were studied, a number of additional differences became apparent when patients were examined in their six age-severity sub-groups. These differences are shown in table 17 which reveals that, in general after one week imipramine tended to be slightly more effective than amitriptyline in alleviating the depressive symptoms of young clinically-mild, young clinically-severe and

middle-aged clinically-mild patients; on the other hand, in middle-aged clinically-severe, elderly clinically-mild and elderly clinically-severe cases, amitriptyline was superior.

TABLE 17

MEAN FIRST-WEEK IMPROVEMENT SCORES IN 17 DEPRESSIVE SYMPTOMS

	DEPRESSIVE SYMPTOM	RANGE OF SCORES	"YOUNG" (30-49) CL-MILD (Score 0-49)		"YOUNG" (30-49) CL-SEVERE (Score 50+)		"MIDDLE-AGED (50-59) CL-MILD (Score 0-49)		"MIDDLE-AGED (50-59) CL-SEVERE (Score 50+)		"ELDERLY" (60-70) CL-MILD (Score 0-49)		"ELDERLY" (60-70) CL-SEVERE (Score 50+)		TOTAL GROUP	
			Amit. (n=11)	Imip. (n=11)	Amit. (n=11)	Imip. (n=12)	Amit. (n=15)	Imip. (n=12)	Amit. (n=13)	Imip. (n=10)	Amit. (n=11)	Imip. (n=12)	Amit. (n=8)	Imip. (n=11)	Amit. (n=69)	Imip. (n=68)
1	Depressed Mood	0-8	1.3	2.3	1.3	2.0	.3	.8	2.3*	1.0	1.1	1.3	1.9	.8	1.3	1.4
2	Retardation	0-8	.7	1.6	1.4	1.0	.2	.4	.9	.7	1.1	.6	.9	-.1	.8	.7
3	Work and Interests	0-8	1.6	2.2	1.5	2.7	.7	1.0	2.0	1.2	1.1	1.5	2.6*	.9	1.5	1.6
4	Guilt	0-8	.9	.4	1.2	1.9	-.3	.3	1.3	1.7	.2	.2	2.1	.8	.8	.9
5	Suicide	0-8	2.2	2.5	2.1	3.1	2.2	2.0	3.0	2.1	.9	.8	3.1	2.4	2.2	2.1
6	Anxiety, psychic	0-8	2.1	1.9	1.6	2.2	1.0	.7	2.3	1.6	1.8	1.4	2.6	1.1	1.8	1.5
7	Anxiety, somatic	0-8	.9	1.4	2.2	1.8	1.7	1.0	2.7	1.7	1.3	.5	2.6	1.6	1.9	1.3
8	Hypochondriasis	0-8	.5	.5	0	2.3*	1.1	.4	.9	.3	.9	0	.4	2.2	.7	1.0
9	Agitation	0-4	.3	.4	.5	1.4	1.0	1.0	2.3	1.5	.5	.8	2.6	1.3	1.2	1.1
10	Insomnia, initial	0-4	1.6	.4	1.7	1.2	.6	1.4	1.6*	-.2	.7	.7	.4	1.2	1.2	.8
11	Insomnia, middle	0-4	0	.2	-.2	-.2	.1	.3	1.3	1.5	.6	.2	2.6*	-.1	.6	.3
12	Insomnia, delayed	0-4	0	-.4	.4	.2	.6	-.7	1.5	.5	.1	-.5	0	.3	.5*	-.1
13	Somatic symptoms, gastrointestinal	0-4	.9	1.1	1.1	1.2	1.0	-.2	1.7	1.4	1.5	.3	1.2	.4	1.2*	.7
14	Somatic symptoms, general	0-4	.6	1.5	1.3	1.1	.2	.5	1.1	.8	.4	.5	1.7	1.4	.8	.9
15	Genital symptoms	0-4	1.4	1.0	1.4	.7	.3	-.3	.9	.9	.3	-.1	.7	-.2	.8	.3
16	Loss of Weight	0-4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	Loss of insight	0-4	0	0	.5	.7	.1	0	.4	-.2	.3	.4	.6	-.3	.3	.1
	TOTALS:	0-100	15.0	17.0	18.0	23.3	10.8	8.6	26.2	16.5	12.8	10.1	26.0*	13.7	17.6	13.6

* Significant at the 5 per cent level.

Since it appeared possible that the first-week improvement registered by the total one-week difference scores might be related to outcome in terms of discharge or ECT, table 18 was constructed, percentage improvement being used to allow for the effect of differing initial scores.

TABLE 18

OUTCOME OF TREATMENT IN 137 HOSPITALIZED FEMALE DEPRESSIVES
ACCORDING TO PERCENTAGE IMPROVEMENT IN INITIAL SCORES AFTER 1 WEEK.

CATEGORY OF PATIENT	OUTCOME	% IMPROVEMENT ON AMITRIPTYLINE(n=69)							% IMPROVEMENT ON IMIPRAMINE (n=68)						
		Below 10	10-19	20-29	30-39	40-49	50-59	Above 60	Below 10	10-19	20-29	30-39	40-49	50-59	Above 60
YOUNG CLINICALLY-MILD (Aet 30-49, scale score 0-49)	DISCHARGE	2	1	-	1	1	1	4	-	1	2	-	2	1	2
	E. C. T.	-	-	-	1	-	-	-	1	-	-	1	1	-	-
YOUNG CLINICALLY-SEVERE (Aet 30-49, scale score 50 +)	DISCHARGE	-	2	1	1	1	1	1	1	1	-	1	2	-	2
	E. C. T.	2	-	1	-	-	1	-	1	-	1	-	1	1	1
MIDDLE-AGED CLINICALLY-MILD (Aet 50-59, scale score 0-49)	DISCHARGE	4	2	-	4	1	-	2	1	1	1	1	1	1	2
	E. C. T.	-	-	-	1	1	-	-	2	-	1	-	-	1	-
MIDDLE-AGED CLINICALLY-SEVERE (Aet 50-59, scale score 50 +)	DISCHARGE	-	-	1	4	1	4	1	-	1	-	2	-	-	2
	E. C. T.	-	1	1	-	-	-	-	3	-	1	-	-	-	1
ELDERLY CLINICALLY-MILD (Aet 60-70, scale score 0-49)	DISCHARGE	1	-	3	-	1	2	2	2	2	-	-	1	-	2
	E. C. T.	1	-	1	-	-	-	-	2	-	1	1	-	-	1
ELDERLY CLINICALLY-SEVERE (Aet 60-70, scale score 50 +)	DISCHARGE	-	-	-	1	2	-	3	-	-	-	-	-	2	-
	E. C. T.	-	1	1	-	-	-	-	3	3	2	1	-	-	-
TOTAL GROUP	DISCHARGE	7	5	5	11	7	8	13	4	6	3	4	6	4	10
	E. C. T.	3	2	4	2	1	1	0	12	3	6	3	3	1	3

When the bottom rows of figures in table 18 are inspected, it can be seen that, in the case of amitriptyline, as the percentage of first week improvement increased, the numbers discharged increased and the numbers receiving ECT decreased. This trend was not so clearly evident with imipramine. Moreover when a level of 30 per cent of improvement was chosen it was evident that at and above this level the depressive state of all patients over 60 and all clinically-severe patients over 50 were relieved by amitriptyline, a development which did not occur in imipramine-treated patients. Nevertheless, the figures in table 18 reveal that the outcome in terms of discharge i.e. drug success of all patients who attained a 30 per cent or greater improvement in the first week was significantly better in both drug groups (amitriptyline $p = .02$, imipramine $p = .015$). When the number of patients who improved 30 per cent or more on amitriptyline were compared with those who improved to a

similar extent on imipramine, the superior drug response rate of the amitriptyline-treated group was statistically significant ($p = .05$); further, so uniformly effective was amitriptyline that 26 patients who did not reach the 30 per cent level still fared better than 34 corresponding patients on imipramine, the trend almost attaining statistical significance ($p = .07$). For patients treated with amitriptyline, therefore, a 30 per cent or greater improvement in Hamilton score after one week of treatment appeared to be a useful prognostic indicator; at this level the correlation with successful outcome was .28, a figure significant at the 5 per cent level.

To what extent was the 30 per cent or more scale score improvement reflected in changed scores on the overall clinical assessments? These five-point assessments were made by each of the two physician raters (A.H. and C.G.B.) after completion of the Hamilton scale; totalling their two assessments to obtain the score, the range ran from zero to eight. The correlation between the overall assessments and the Hamilton score for the 69 amitriptyline-treated patients, both initially and after one week, was .6. The percentage improvement in overall assessment during the first week of treatment was computed for the amitriptyline patients; a 30 per cent or greater improvement in overall clinical assessment was correlated with outcome in terms of recovery without ECT at the level of .23, a figure which just missed statistical significance ($p = .06$). It is apparent, therefore, that whilst improvement in the overall clinical assessments did not quite predict outcome to a statistically significant degree, improvement in the Hamilton scale scores did predict outcome significantly. This finding suggests that the Hamilton scale was a more useful instrument for prediction than the overall clinical assessment.

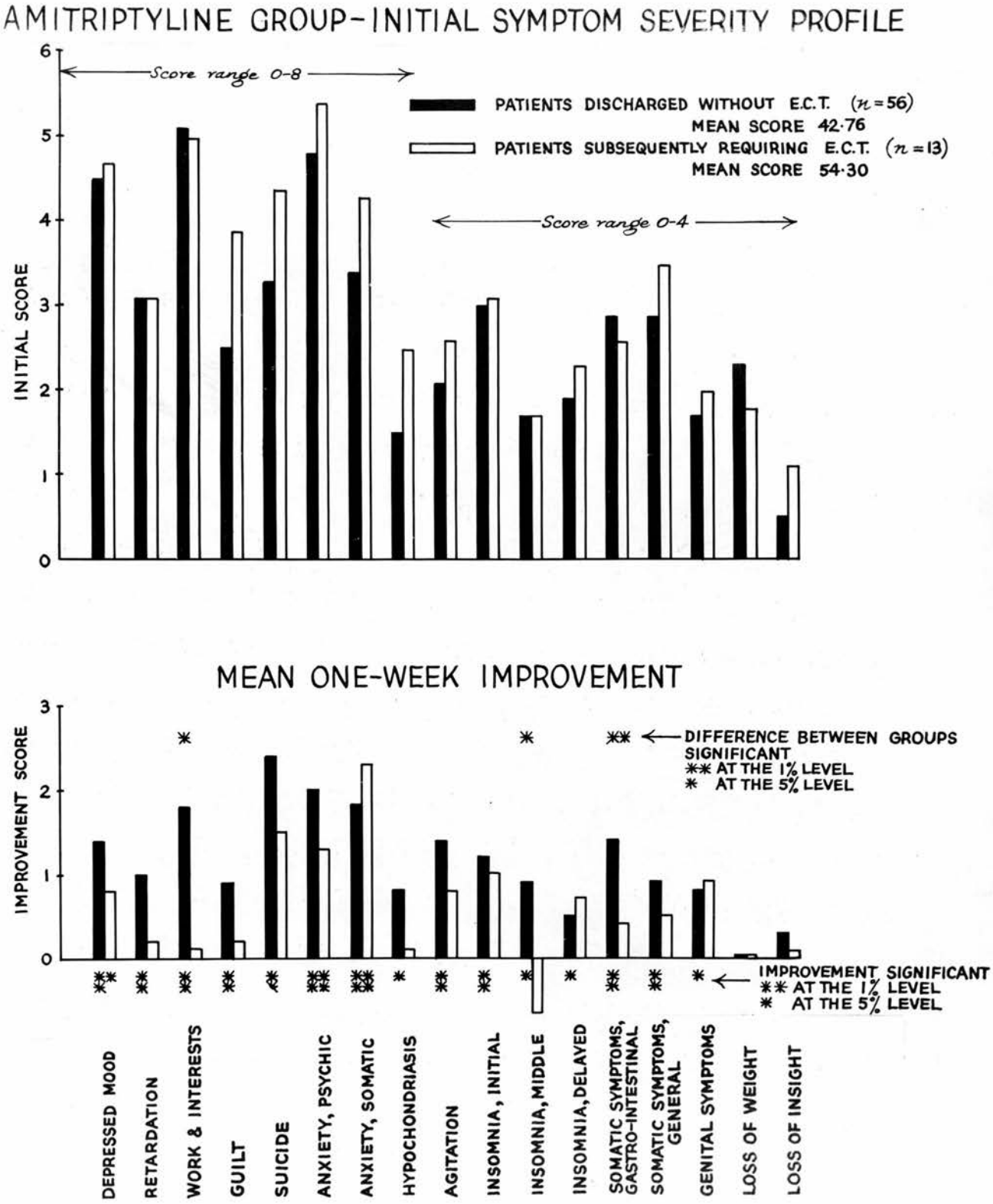
An approximate idea of the probability of recovery without ECT on the two drugs can be gained from an inspection of table 18. The most important features of this table can be summarized as follows: in the amitriptyline group, the 30 per cent level of first-week improvement heralded recovery without ECT in all patients between 60 and 70, in all those over 50 who were clinically-severely depressed, in 87 per cent of the young clinically-mild, in 80 per cent of the young clinically-severe and in 78 per cent of the middle aged clinically-mild depressives. In the imipramine group, the 30 per cent level of first week improvement presaged recovery without ECT in only 62 per cent of the elderly patients, in 75 per cent of the clinically-severe depressives over 50, in 71 per cent of the young clinically-mild cases, in 62 per cent of the young clinically-severe patients and in 83 per cent of those in the middle-aged clinically-mild group.

AMITRIPTYLINE-RESPONSIVE GROUPS OF PATIENTS

Although table 18 demonstrates that amitriptyline produced better results than imipramine in every group of patients included in the trial, its superiority was particularly striking in patients over 60 and those over 50 with clinically-severe depressions. The mean initial symptom severity scores (57.07) of these three groups of patients combined (i.e. the middle-aged clinically severe, the elderly clinically-mild and the elderly clinically-severe) was higher than that of the three groups of patients in which the superiority of amitriptyline was not so well marked (i.e. the young clinically-mild, the young clinically-severe and the middle-aged clinically-mild, with a mean of 43.37). Further, the one-week improvement score of the former group (21.78) in which the 30 per cent level was of prognostic value, was not as high as that of the latter group (14.96) in which this did not to the same extent apply.

AMITRIPTYLINE RESPONDERS AND NON-RESPONDERS

FIGURE 15



The 56 amitriptyline responders who were discharged without ECT were compared with the 13 non-responders who subsequently required that physical treatment. In socio-economic and psychiatric background, there were no significant differences nor were differences in Hobson scale scores evident. On the other hand, the initial symptom severity scores and the one-week difference scores in the two groups of patients were noticeably dissimilar.

Initially, the non-responders were more severely ill (though not significantly so) in respect of guilt, suicidal proclivities, psychic anxiety, hypochondriasis, agitation, terminal insomnia, general somatic symptoms and loss of insight. After one week of treatment the groups differed more markedly still. Whereas the responders had improved significantly on all the symptoms enumerated in Hamilton's scale except two (loss of weight and loss of insight), the non-responders had improved significantly on only three - depressed mood, psychic anxiety and somatic anxiety. Three symptoms at this time significantly differentiated responders from non-responders: non-responders showed significantly less improvement in gastro-intestinal somatic symptoms ($p < .01$), middle insomnia ($p < .05$) and reduction in work and interests ($p < .05$). In other words, responders could be differentiated from non-responders after one week of treatment by exhibiting, unlike the latter, a better appetite, more restful sleep and some return of interests and the capacity to work. In this connection, it is worth noting that, as figure 15 shows, whilst the rapidly-evident tranquillising action claimed for amitriptyline was clearly apparent, it was of no value in forecasting outcome, for both responders and non-responders improved markedly in psychic and somatic anxiety, and their respective improvements in agitation were not clinically distinguishable.

In addition to these differences in severity of symptoms, as noted earlier, significantly fewer amitriptyline responders showed delusions during their period of hospitalization ($p < .01$).

LENGTH OF HOSPITAL STAY

In order to assess how the length of hospitalization of patients treated with amitriptyline and imipramine compared with the length of stay of patients treated with electroconvulsive therapy, a control group of 60 patients was chosen from depressed patients treated in the hospital a year before the study. These patients were matched with the drug groups in regard to the proportions of endogenous and reactive cases in each age decade. All 60 had been considered sufficiently ill to require electroconvulsive treatment; 39 had been given ECT as their sole treatment, whilst 21 had received ECT in conjunction with imipramine. Analysis of the time the various groups of patients spent in hospital revealed that there were no significant differences between the median number of days for those who recovered on the drugs and the control group (amitriptyline 37 days, imipramine 31 days, control group 34 days, with 32 days for ECT alone and 36 days for ECT in conjunction with imipramine). The patients who failed to recover with drugs stayed longer; the median length of stay for the failures on amitriptyline was 60 days and for imipramine 62 days.

SUMMARY

The findings in the second phase of the investigation corresponded closely with the earlier results, confirming the superiority of amitriptyline. In the total sample of 137 hospitalized female depressives 56 (81%) of 69 treated with the drug recovered without ECT in contrast to 37 (54%) of 68 receiving imipramine ($p < .002$). Side effects did not

pose a serious problem though one death was probably attributable to imipramine.

The socio-economic and psychiatric background of the patients was unremarkable. When their initial individual depressive symptom scores were analysed however, it was found that depressed mood, agitation, delayed insomnia and loss of weight increased significantly with age and that agitation, guilt, suicidal proclivities, loss of insight and hypochondriasis showed a disproportionately large increase with increase in overall severity.

Using the criterion of discharge without ECT or recourse to this treatment, several variables were studied to determine their prognostic significance. It was found that:

(i) the Hobson scale score - was of no predictive value with either drug.

(ii) initial severity of depressive symptoms - did not affect the response to amitriptyline but with several symptoms adversely affected the response to imipramine. Amitriptyline was more effective than imipramine in patients with severe depressive symptoms.

(iii) delusions - if present lessened the effectiveness of amitriptyline and nullified the effectiveness of imipramine.

(iv) age, menopausal state, type of depression and severity - affected the response to the two drugs. Amitriptyline was significantly more effective than imipramine in patients over 50 years of age, in those who were postmenopausal, those who were endogenously depressed and those who had severe

depressions. Imipramine was significantly less effective in severe depressives than in milder cases, especially in patients over the age of 50. Age, menopausal state and type of depression were highly intercorrelated i.e. patients over 50 were usually postmenopausal and tended to suffer from endogenous depressions, but none of the three variables correlated appreciably with severity of illness. An analysis of variance in 120 of the 137 patients revealed a highly significant difference between drugs in favour of amitriptyline and a significant interaction between drugs and severity of illness.

(v) first-week response to drug treatment - for both drugs was significantly correlated with outcome. Thirty-nine of 56 patients responding to amitriptyline showed a 30 per cent or greater improvement in Hamilton score after one week. This level of improvement was followed by recovery without ECT in all patients over 60 and in all those over 50 with severe depression. On the Hamilton scale the 56 amitriptyline responders in comparison with the 13 non-responders were initially less severely ill though this was not clinically distinguishable; after a week, however, non-responders could readily be differentiated by their failure to improve in three symptoms - gastro-intestinal somatic symptoms, middle insomnia, and reduced work and interests. The early tranquillizing action of amitriptyline was valueless in predicting outcome. Patients successfully treated with amitriptyline spent no longer in hospital than did a matched retrospective group treated with ECT.

CHAPTER IV.

FACTOR ANALYSIS OF INITIAL SYMPTOMATOLOGY

The Hamilton scale ratings of the initial severity of the depressive symptoms of the 137 patients included in the investigation were factor analysed. Lawley's Maximum Likelihood Method, which includes a test of the significance of the residuals was used. The results indicated that four factors were sufficient to account for the variance, leaving a non-significant set of residuals. The Maximum Likelihood Solution was rotated, using a quartimax procedure. Finally, the rotated factor scores for each patient were computed according to the matrix formula $ZR^{-1}F$ where Z is a matrix of standard scores calculated from the raw scores, F is the matrix of the rotated factor loadings and R^{-1} is the inverse of the correlation matrix with communalities in diagonal.

TABLE 19

CORRELATION MATRIX OF HAMILTON SCALE SCORES ON 137 DEPRESSED WOMEN

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
(1)	Depressed Mood	1.00	0.52	0.60	0.46	0.36	0.33	0.16	0.03	0.44	0.17	0.28	0.19	0.29	0.31	-0.09	0.18	0.44
(2)	Retardation		1.00	0.41	0.30	0.09	0.10	-0.04	0.07	0.19	0.03	0.24	0.18	0.15	0.35	0.01	0.07	0.26
(3)	Work and Interests			1.00	0.34	0.17	0.29	0.08	0.13	0.33	0.20	0.16	0.29	0.30	0.45	-0.01	0.15	0.33
(4)	Guilt				1.00	0.49	0.49	0.24	0.11	0.44	0.18	0.19	0.12	0.14	0.24	0.11	0.22	0.47
(5)	Suicide					1.00	0.31	0.31	0.20	0.26	0.11	0.07	0.09	0.12	0.20	0.09	0.12	0.21
(6)	Anxiety, psychic						1.00	0.59	0.28	0.45	0.32	0.18	0.05	0.20	0.22	0.05	0.18	0.19
(7)	Anxiety, somatic							1.00	0.31	0.29	0.25	0.12	-0.02	0.21	0.25	0.15	0.07	0.03
(8)	Hypochondriasis								1.00	0.22	0.17	0.06	-0.00	0.16	0.17	0.02	0.10	0.10
(9)	Agitation									1.00	0.29	0.20	0.21	0.20	0.11	-0.12	0.14	0.19
(10)	Insomnia, initial										1.00	0.04	0.20	0.24	0.20	0.15	0.10	-0.05
(11)	Insomnia, middle											1.00	-0.18	0.14	0.20	0.01	0.01	0.19
(12)	Insomnia, delayed												1.00	0.05	0.09	0.02	0.01	0.04
(13)	Somatic symptoms, gastrointestinal													1.00	0.22	0.17	0.17	0.10
(14)	Somatic symptoms, general														1.00	0.14	0.10	0.09
(15)	Genital symptoms															1.00	-0.00	0.14
(16)	Loss of Weight																1.00	0.16
(17)	Loss of insight																	1.00

Table 19 shows the correlation matrix of the seventeen factors in the 137 patients. The saturations of the unrotated factors are shown in table 20.

TABLE 20

SATURATIONS OF UNROTATED FACTORS

		Factor 1	Factor 2	Factor 3	Factor 4
(1)	Depressed mood	0.75	-0.33	-0.02	0.10
(2)	Retardation	0.47	-0.43	0.11	-0.07
(3)	Work and interests	0.65	-0.35	0.25	0.07
(4)	Guilt	0.70	0.04	-0.35	-0.16
(5)	Suicide	0.48	0.15	-0.18	-0.15
(6)	Anxiety, psychic	0.65	0.46	-0.02	0.05
(7)	Anxiety, somatic	0.44	0.61	0.16	-0.07
(8)	Hypochondriasis	0.26	0.27	0.12	-0.01
(9)	Agitation	0.60	0.12	-0.13	0.39
(10)	Insomnia, initial	0.33	0.22	0.22	0.14
(11)	Insomnia, middle	0.31	-0.06	0.01	-0.07
(12)	Insomnia, delayed	0.22	-0.16	0.09	0.20
(13)	Somatic symptoms, gastrointestinal	0.36	0.01	0.24	-0.01
(14)	Somatic symptoms, general	0.46	-0.08	0.45	-0.27
(15)	Genital symptoms	0.06	0.13	0.09	-0.42
(16)	Loss of weight	0.25	0.01	-0.06	-0.02
(17)	Loss of insight	0.47	-0.24	-0.33	-0.24

The rotated factor saturations are indicated in table 21; in this, the items in the scale have been rearranged to enable delineation of the factors in terms of individual items with saturations of over 0.20.

TABLE 21

SATURATIONS OF ROTATED FACTORS

		Factor 1	Factor 2	Factor 3	Factor 4
(3)	Work and interests	0.10	0.77	-0.08	0.04
(1)	Depressed mood	0.15	0.79	0.16	-0.12
(2)	Retardation	-0.09	0.63	0.07	0.09
(12)	Insomnia, delayed	0.01	0.30	-0.11	-0.13
(11)	Insomnia, middle	0.12	0.27	0.09	0.05
(17)	Loss of insight	0.02	0.43	0.52	0.02
(5)	Suicide	0.37	0.25	0.33	0.02
(4)	Guilt	0.39	0.45	0.53	-0.06
(9)	Agitation	0.44	0.41	0.05	-0.42
(13)	Somatic symptoms, gastrointestinal	0.23	0.33	-0.11	0.11
(14)	Somatic symptoms, general	0.22	0.49	-0.13	0.44
(7)	Anxiety, psychic	0.74	0.25	0.12	-0.07
(6)	Anxiety, somatic	0.76	0.03	-0.03	0.13
(10)	Insomnia, initial	0.39	0.19	-0.19	-0.02
(8)	Hypochondriasis	0.38	0.08	-0.05	0.01
(15)	Genital symptoms	0.13	-0.04	0.14	0.40
(16)	Loss of weight	0.14	0.18	0.12	-0.02

The rotated factor scores of the 137 patients were examined in relation to age, severity, type of depression, the presence of delusions, and outcome with amitriptyline or imipramine. Each of the five variables was dichotomized as follows (1) age - "young" (30-49) versus "old" (50-70), (2) severity - "clinically-mild" (scale score 0-49) versus "clinically-severe" (score 50-100), (3) type of depression - endogenous versus reactive, (4) delusions - deluded versus non-deluded and (5) outcome with amitriptyline or imipramine - discharged on maintenance doses of the appropriate drug or referred for E.C.T. The frequency distributions of the factor scores of every patient on each variable was compared, the significance of the differences

that were found being assessed by means of chi-square. Where differences were very marked, the phi-coefficient (of correlation) was computed. The results that were obtained are shown in table 22.

TABLE 22

RELATIONSHIP BETWEEN FACTOR SCORES AND OUTCOME

	ITEM LOADINGS		EFFECT OF AGE	EFFECT OF SEVERITY	EFFECT OF TYPE OF DEPRESSION	EFFECT OF DELUSIONS	OUTCOME WITH DRUGS
FACTOR 1	Anxiety, somatic Anxiety, psychic Agitation Insomnia, initial Guilt Hypochondriasis Suicide Somatic, g.i. Somatic, gen.	0.76 0.74 0.44 0.39 0.39 0.38 0.37 0.23 0.22	Older patients had higher scores. ($p = .06$, $\phi = .16$)	More severely ill patients had higher scores. ($p < .001$, $\phi = .46$)	Nil	Nil	Amitriptyline was superior to imipramine in patients with positive scores. ($p = .02$)
FACTOR 11	Depressed mood Work and interests† Retardation Somatic, gen. Guilt Loss of insight Agitation Somatic, g.i. Insomnia, delayed Insomnia, middle	0.79 0.77 0.63 0.49 0.45 0.43 0.41 0.33 0.30 0.27	Nil	More severely ill patients had higher scores. ($p < .001$, $\phi = .47$)	Endogenous depressives had higher scores. ($p < .001$, $\phi = .36$)	Deluded patients had higher scores. ($p < .001$, $\phi = .43$)	Amitriptyline was superior to imipramine in patients with positive scores ($p < .001$). For imipramine, a high score carried a poorer chance of response. ($p < .01$)
FACTOR 111	Guilt Loss of insight Suicide	0.53 0.52 0.33	Nil	More severely ill patients tended to have higher scores ($x^2 = 2$, $p = .16$)	Endogenous depressives tended to have higher scores ($p = .08$)	Deluded patients had higher scores ($p < .001$, $\phi = .29$)	Nil
FACTOR 1V	Somatic, gen. Genital Agitation	0.44 0.41 -0.42	Older patients had lower scores	Nil	Endogenous depressives tended to have low scores ($p = .08$)	Nil	Nil

Factor 1, with high saturations of somatic anxiety, psychic anxiety and agitation, contains a number of items that could as well be found in a severe anxiety state as in an agitated depression. The absence of depression makes it impossible to label the factor "agitated depression"; further, if the factor had corresponded to the latter entity, a significant difference in type of depression and, perhaps, on delusions, would have been evident in table 22 since agitated depressions were invariably diagnosed as endogenous. Factor 1 must therefore be regarded as an anxiety-agitation syndrome in which older and more severely ill patients showed significantly higher scores and in the treatment of which amitriptyline was superior to

imipramine. One of the four symptoms that were earlier found to increase significantly with age - agitation, delayed insomnia, loss of weight and depressed mood - was present in factor 1, in addition to four of the five symptoms which increased disproportionately with increasing overall severity - agitation, guilt, suicidal proclivities, hypochondriasis and loss of insight. The effect of increase in age and increase in overall severity in the factor 1 score is thus readily comprehensible, as also the fact that high scores were correlated with age and severity (ϕ = .16 and .46). Further, the earlier investigation had demonstrated that patients with severe degrees of five of the individual symptoms in factor 1 - psychic anxiety, agitation, initial insomnia, gastrointestinal somatic symptoms and general somatic symptoms - showed a significantly better response to amitriptyline than to imipramine. The findings regarding the superiority of amitriptyline in patients with positive scores on factor 1 therefore appear consistent with the results obtained earlier.

Factor 2, with high loadings of depressed mood, reduced work and interests, retardation, general somatic symptoms and guilt, appears to correspond to an endogenous depression of the retarded type. It is interesting, moreover, that in this factor also, agitation had a high saturation. The scores on this factor were unaffected by age but they increased with increasing severity and were higher in endogenous depressives and in those who were deluded; patients with positive scores responded significantly better to amitriptyline than imipramine and a high score carried a significantly poorer prognosis with the latter drug. On inspection it is apparent that factor 2 contains three of the four symptoms found to increase significantly with age, but their contribution is evidently not sufficiently great to render the factor age-susceptible. On clinical grounds this seems quite reasonable,

for endogenous depressives manifesting the symptoms contained in factor 2 would not be expected to have higher scores when aged between 50 and 70 than those 30 to 49. On the other hand the factor-scores increased significantly with severity, though only guilt and agitation of the five symptoms found to increase disproportionately with increase in overall severity, were contained within it. As in factor 1, there was an appreciable correlation (ϕ = .47) between severity and level of score. The higher score shown by deluded patients on factor 2 and their phi-coefficient of .43 is comprehensible on clinical grounds, for delusions are a not uncommon symptom in severe endogenous depressives. Again, the superiority of amitriptyline over imipramine in patients with positive scores on factor 2 is understandable, for amongst patients with severe degrees of all the symptoms (except guilt) contained in this factor, amitriptyline had earlier been found to be associated with a significantly better prognosis than imipramine. Finally, the adverse prognostic significance, for imipramine, in patients with high scores on factor 2, could be linked with the earlier observation that severity in four symptoms contained in it - depressed mood, reduction of work and interests, retardation and agitation - carried a significantly worse prognosis with this drug.

Factor 3 does not appear to correspond to any known clinical entity, though for convenience it might be thought of as "delusional guilt". More severely ill and endogenous depressives tended to have higher scores whereas deluded patients definitely had higher scores, the factor correlating with delusions at the level of .29. Since, in the patients studied, delusions had been rather commoner in those over 50 than in those under 50 years of age, scores on factor 3 could have been expected to change significantly with age.

This was not the case, nor did the factor reflect differences between drugs, though four out of ten deluded patients had responded to amitriptyline in contrast to none out of seventeen similar patients receiving imipramine.

Factor 4, again, resists allocation to a clinical category. The marked affect of age on this factor can be understood in that in the earlier part of the investigation genital symptoms had been found to decrease significantly with increasing age whilst the reverse obtained for agitation. Table 22 shows that endogenous depressives tended to have a low score on factor 4, suggesting that its positively loaded symptoms are more commonly found in reactive depressives who, the earlier part of the investigation had shown, tended to be younger.

OTHER FACTOR-ANALYTIC STUDIES

Although the results of the (rotated) factor analysis appear to make clinical sense and to tie together the findings of the earlier part of the investigation, it is of interest to compare them with those obtained in three factor analytic studies of depression carried out by Hamilton (1960) Hamilton and White (1959) and Grinker, Miller, Sabshin, Nunn and Nunnally (1961).

Factor 1 in the present study - an anxiety agitation factor which was reminiscent of agitated depression without depression - broadly corresponds to Hamilton's factor 2. Hamilton also remarks on the absence of depression in this factor. Factor 2 in the present study - which clinically suggested an endogenous depression with retardation - resembles Hamilton's factor 1. There was no resemblance between Hamilton's third and fourth factors and the corresponding factors found in the present study. In general, however, it seems possible that the symptoms of depression are not identical

in the two sexes - depressed women, for instance, lose their sexual desire with increasing age to a greater extent than men and may be more prone to develop agitated depressions. In view of the fact that whilst Hamilton's analysis utilized 49 depressed men in England, the present analysis was made on 137 depressed women in Australia, the correspondence between the findings is satisfactory.

Later, Hamilton and White (1959), examining clinical syndromes in depressive states, classified 64 male patients on aetiological grounds into four groups: Endogenous, Doubtful Endogenous, Doubtful Reactive and Reactive Depressions. They found that, in addition to differing significantly in their total scale score, the means of the four groups differed significantly in their scores on the first factor of the scale (factor 2 in the present study). This demonstrated, Hamilton and White state, that endogenous depression was more severe than reactive and that the first factor, which appeared to be a measure of retarded depression, was also a measure of endogenous depression. These findings correspond to those obtained in regard to factor 2 in the present study. Hamilton and White also found that agitated depressives had high scores on factor 2 (factor 1 in the present study). Factor 3, on which both retarded and agitated patients had high scores, had the highest correlation with outcome. High scores on factor 4 were found in depressed patients who had abnormal personalities and further investigation of this group suggested that the factor might correspond to "psychopathic" depression.

The study carried out by Grinker et al. was made on patients of both sexes in the United States and is less easy to compare with the present investigation since Hamilton's scale was not used. Fifteen factors

were obtained by analysing the results of a "feelings and concern" check list (five factors) together with a "current behaviour" check list (ten factors) in 96 depressed patients. The fifteen factors were combined to produce four factor-patterns (A) Feelings - dismal, hopeless, loss of self-esteem, slight guilt feelings; behaviour - isolated, withdrawn, apathetic, speech and thinking slowed, with some cognitive disturbances (B). Feelings - hopeless with low self-esteem, considerable guilt feelings, high anxiety; behaviour - agitation and clinging demands for attention. (C) Feelings - abandonment and loss of love; behaviour - agitated, demanding, hypochondriacal and (D) Feelings - gloom, hopelessness and anxiety; behaviour - demanding, angry, provocative. Grinker et al's factor pattern A would seem to correspond broadly to factor 2 of the present study. Patterns B and C both appear to resemble the present study's factor 1, whilst the feelings and behaviour characteristic of pattern D could be found in either factors 1 or 2.

SUMMARY

A factor analysis was carried out of the initial symptomatology of the 137 patients, using the ratings provided by Hamilton's depressive scale. Four factors were isolated which accounted for most of the variance and left a non-significant set of residuals. The rotated factors were examined since clinically they were the most meaningful; differences in factor scores in relation to age, severity, type of depression, the presence of delusions and outcome of treatment with amitriptyline and imipramine were scrutinized. Factor 1, a syndrome of anxiety and agitation, yielded scores which rose significantly with age and increasing severity; amitriptyline was superior to imipramine in patients with positive scores. Factor 2, which

appeared to correspond to retarded endogenous depression, yielded scores which were significantly higher in endogenous depressives, those who were severely ill and those who were deluded; amitriptyline was superior to imipramine in patients with positive scores and, for the latter drug, a high score carried a poor prognosis. Factor 3, a syndrome of "delusional guilt", yielded scores which were significantly higher in deluded patients and tended to be higher in those who were endogenously depressed and those who were severely ill. Factor 4, which contained positive saturations of general somatic and genital symptoms and a negative saturation of agitation, did not correspond to any clinical entity; it yielded scores which were significantly lower in older patients and tended to be low in those who were endogenously depressed.

CHAPTER V.

RESULTS OF THE FOLLOW-UP

One advantage antidepressant drugs are said to possess over electroconvulsive therapy is the reduced risk of relapse associated with continued maintenance dosage. At the conclusion of the in-patient phase of the investigation, amitriptyline, to which 56 (81%) of 69 patients had responded, was significantly more effective than imipramine, to which 37 (54%) of 68 patients responded. How did the two drugs compare over the period of follow-up?

With occasional exceptions, all the 93 patients responding to the two drugs were discharged on maintenance doses of 100 mg. daily. Patients were seen two weeks, six weeks, three months and six months after discharge, or more frequently if their condition warranted it. Three and six months after leaving hospital, they were rated independently on Hamilton's scale by two physicians (A.H. and C.G.B.) at a joint interview. During the interview information was gathered regarding significant events in their life since leaving hospital, their level of activity, their persistence in taking the medication and their need for hypnotics. In addition, patients were weighed and a note was made of spontaneous comments in regard to their condition and the side effects, if any, that had troubled them. As in the in-patient part of the trial, a double-blind technique was used.

The 44 patients who, not responding to amitriptyline or imipramine, had had to receive ECT, were also followed up. They were seen regularly in the out-patient department but only rated on one occasion, six months after discharge. The ratings were carried out in the same way as with the drug-responders; the two physicians making them were not aware to

which drug the patient had failed to respond. Weights and salient personal details were recorded.

Table 23 shows the results in 120 patients followed up for a period of six months (86% of the sample). Seventeen patients (12%), for the following reasons, had to be excluded: (1) No contact at six months - six patients (11) Follow-up incomplete when study terminated - six patients (111) Maintenance treatment contra-indicated - three patients on amitriptyline; two became hypomanic and one developed glaucoma the day after discharge (1V) Maintenance medication given to ECT cases - one patient given amitriptyline after ECT in view of her previous history of early relapse and (V) Failure to continue taking medication - one patient on imipramine also stopped taking her capsules two months after discharge.

TABLE 23

RESULTS OF FOLLOW UP IN 120 PATIENTS

CONDITION OF THE PATIENT	AMITRIPTYLINE (n = 62)		IMIPRAMINE (n = 58)	
	RESPONDERS: DISCHARGED ON DRUG	NON-RESPONDERS: DISCHARGED OFF DRUG AFTER ECT	RESPONDERS: DISCHARGED ON DRUG	NON-RESPONDERS: DISCHARGED OFF DRUG AFTER ECT
INITIALLY - Well	50	12	34	24
AFTER - Well	45	10	28	21
THREE - Relapsed	3	2	5	3
MONTHS - Manic Episode	2	0	1	0
AFTER - Well	42 (84%)	6	27 (79%)	14
SIX - Relapsed	6*	6	6**	10
MONTHS - Manic Episode	2	0	1	0

* includes one death

** includes two deaths from suicide

In table 23 "well" means the patient was living out of hospital, usually symptom free or with minimal symptoms. The quality of the remission on discharge and after six months will shortly be described in more detail. "Relapsed" connotes a recrudescence of depressive symptoms within six months of discharge, to an extent necessitating further psychiatric treatment as an in-patient. "Manic episode" denotes readmission in a state of mania.

Table 23 shows that there was very little difference between the two drug-responsive groups at three and six months, the percentage of patients remaining well on amitriptyline (84%) being slightly, though not significantly, higher than those on imipramine (79%).

PATIENTS REMAINING WELL

The majority of patients discharged on drugs, excluding those who relapsed or became manic, were symptom free throughout the follow up period. However, there were a few exceptions who, whilst not relapsing, did not achieve or maintain a completely satisfactory remission.

Of the 42 patients discharged on amitriptyline who were well after six months, there were eight whose condition at this time was not totally satisfactory; three of these were unsatisfactory when they left hospital. Two patients who developed mild symptoms of relapse responded to a few weeks increase of dosage to 150 mg daily without the need for readmission. Of the 42 patients who were well at six months 35 who were weighed showed a mean gain of 9.6 lb. (range - 8 to +42 lb.). Twelve described their condition in unusually glowing terms and the same number mentioned experiencing side effects - dryness of the mouth, excessive thirst, sweating and an excessive

appetite. Of the 27 patients discharged on imipramine who were well after six months, there were six whose condition was not optimal at this time; all 27 had been quite well on leaving hospital. Again, the majority (79%) of the patients who responded were completely well six months after discharge. Of these 27 patients 25 who were weighed showed a mean gain of 5.4 lb. (range -35 to +24 lb.). This was less but not significantly lower than the increase shown by the amitriptyline patients. Ten of the patients described their condition in glowing terms and eleven mentioned experiencing a mild degree of dryness of the mouth, excessive thirst, sweating and an excessive appetite.

Of 12 amitriptyline-ECT patients, all were well on discharge and one was not altogether satisfactory after six months; of 24 imipramine-ECT patients discharged, two were unsatisfactory at this time and they were joined by four more six months later.

These findings show that the majority of drug responders remain in satisfactory remission for six months if kept on maintenance medication. An appreciably lower proportion of ECT cases remained well in this period.

RELAPSES

In table 23 it can be seen that though relapses in drug responders occurred throughout the six months following discharge, ECT relapses, which were much more frequent, occurred mainly between three and six months after discharge. In each drug group a higher proportion of those who relapsed had had a previous history of depressive illness. With amitriptyline, five out of six relapsers had a previous history versus twelve out of 42 non-relapsers ($p = .06$); with imipramine four out of six relapsers had a previous history versus six out of 27 non-relapsers, ($p = .10$). Further,

whereas only one of the twelve patients relapsing on drugs had been deluded whilst in hospital nine of the sixteen relapsing ECT patients had previously been deluded ($p < .05$). However since of the 27 deluded patients only four, all on amitriptyline, had responded to drugs, the proportion of deluded patients discharged on drugs was much smaller than the proportion discharged after ECT.

The six patients who relapsed on amitriptyline included one young clinically-mild, three young clinically-severe, one old clinically-mild and one old clinically-severe depressive. Five were readmitted and one who relapsed after discontinuing her medication was found dead at home; the cause was uncertain but suicide appeared unlikely. Since four patients were taking amitriptyline when relapse occurred, the relapse rate in those continuing to take the drug was 9 per cent (4 of 46). In four patients no precipitant could be identified whilst in a fifth, who had taken no capsules for three days, severe marital stress was involved. Once in hospital two of the five responded to 200 mg. amitriptyline daily; the third was inadvertently given isocarboxasid and responded to this drug. The fourth and the fifth (in whom a problem of addiction existed) had to be given ECT.

The six patients who relapsed in the imipramine group comprised three old clinically-mild, two young clinically-mild and one old clinically-severe patient. Of these, four were readmitted and two committed suicide at home. One of the latter, believed to have an associated malabsorption syndrome, killed herself whilst taking imipramine. The other, an inadequate personality, was almost immediately readmitted and transferred to a long-stay hospital. There, since she showed no evidence of depression, imipramine was not given; after two months she failed to return from leave and was found dead at home. Since of the four other women admitted to hospital, three were

taking imipramine when they relapsed, the rate of relapse in those continuing to take the drug was 13 per cent (4 of 31). The fourth patient was not taking imipramine, having become hypomanic; she required ECT but the other three patients responded to 200 mg. imipramine daily.

Of the 16 ECT patients who relapsed, one was in the young clinically-mild group, four were in the young clinically-severe group, five were in the old clinically-mild group and six were in the group of old clinically-severe patients.

MANIC EPISODES

Two of the 50 patients discharged on amitriptyline were readmitted in mania during the first three months of the follow-up as well as one of the 34 discharged on imipramine. All three had previously had manic episodes so that neither drug could unequivocally be held responsible. Amongst the remaining 81 patients two, both in the group on imipramine, had previously had an attack of mania; one relapsed into depression during the follow-up and the other remained well.

RESULTS OF ANTIDEPRESSANT THERAPY

Finally it is of interest to compare the results obtained in the present study with those of other investigations. Some of the more important studies that have been carried out are shown in the following table.

TABLE 24

ANTIDEPRESSANT THERAPY : IMMEDIATE AND SIX-MONTH RESULTS

TREATMENT	NUMBER OF PATIENTS		PERCENTAGE RESPONSE	RESPONDING PATIENTS		PERCENTAGE RELAPSE	SOURCE
	Treated	Responding		Followed-up	Relapsing		
AMITRIPTYLINE	69	56	81%	46	4	9%*	Present study 1962
IMIPRAMINE	68	37	54%	31	4	13%	Present study 1962
ECT CONTROL	60	60	100%	60	16	27%	Present study 1961
IMIPRAMINE	81	49	60%	42	6	14%	Kiloh and Ball 1961
IPRONIAZID	30	17	57%	14	2	14%	Kiloh et al. 1960
ECT	52	49	94%	49	24	48%	Kiloh et al. 1960
ECT	219	-	97%	-	-	23%	Thomas 1954
ECT	923	-	82%	-	-	18%	Karagulla 1950
LEUCOTOMY	2637	-	62%	-	-	18%	Tooth and Newton 1961

* Significantly ($p < .05$) lower than ECT Control group.

In table 24 amitriptyline emerges as the most effective drug treatment for depression. Imipramine lags behind, both in the present study and according to the results of the trial carried out by Kiloh and Ball (1961). The findings of a third study show that iproniazid is less effective still (Kiloh, Child and Latner 1960). With ECT the initial results are usually excellent. Nevertheless there is an appreciable rate of relapse with this treatment; so high was this in a group of endogenous depressives treated by Kiloh, Child and Latner that Kiloh and Ball concluded that, six months after treatment, imipramine was as effective as ECT. If this indeed were the case, the present results imply that, after six months, the results obtained with amitriptyline are superior to ECT; but examining the figures in table 24, it is difficult not to conclude that Kiloh, Child and Latner's post ECT relapse rates are unusually high. For this reason, the findings in regard to amitriptyline should also be compared with those obtained in this study's retrospective matched control group treated with ECT and those reported by earlier investigators. (Thomas 1954, Karagulla 1950). This comparison suggests that amitriptyline is initially slightly inferior to ECT, but that

six months after discharge, there is little to choose between the two forms of treatment. The results of leucotomy are appended for general interest; but since patients undergoing this treatment belong to an extremely recalcitrant group, the figures for leucotomy cannot validly be compared with the response to other forms of therapy.

SUMMARY

One hundred and twenty (88%) of the original 137 patients were followed up for six months after leaving hospital. At this time 42 (84%) of the 50 discharged on amitriptyline were well, as were 27 (79%) of the 34 discharged on imipramine. Most of the patients discharged on drugs remained well throughout the period of follow-up. Those on amitriptyline gained an average of 9.6 lb., whilst those on imipramine gained 5.4 lb., a non-significant difference. The quality of the remission produced by the two drugs was identical and with both, side effects were mild and of little consequence. Drug relapses occurred throughout the six months following discharge but ECT relapses, which were considerably more frequent, occurred mainly between three and six months after leaving hospital. On both drugs the majority of relapsers had a previous history of depression; most patients relapsing after ECT had been deluded whilst in hospital. Of six patients relapsing on amitriptyline, one died at home and five were readmitted. Since only four of the six patients were taking amitriptyline when relapse occurred the relapse rate in those who continued to take the drug was 9 per cent (4 out of 46). Three of the five amitriptyline relapsers admitted to hospital responded to 200 mg. of the drug daily. Of six patients relapsing on imipramine two committed suicide and four responded to hospital treatment. Since only four of the six patients were taking imipramine when relapse

occurred the relapse rate in those who continued to take the drug was 13 per cent (4 out of 31). Three of the five imipramine relapsers admitted to hospital responded to 200 mg. daily. The three patients who became manic had all had previous episodes of mania. The results show that amitriptyline, which initially had been more effective than imipramine in the treatment of women hospitalized with depressive states, maintained its superiority throughout a six-month period of follow-up. A comparison of the findings with those of other investigators suggests that amitriptyline, whilst initially slightly less effective than ECT, achieves comparable results six months after the completion of in-patient treatment.

C H A P T E R VI.

DISCUSSION OF THE FINDINGS

The findings of the investigation can conveniently be considered in relation to the phenomenology of depression and the current treatment of severe depressive states.

THE PHENOMENOLOGY OF DEPRESSION

The writers of antiquity have provided so many descriptions of depression that, as Lewis (1934a) has observed, in many ways the history of melancholia is the history of psychiatry. Kraepelin (1921) early provided a comprehensive description of melancholic conditions in mental hospital patients which has not been added to by later writers. Indeed a group of American investigators recently went so far as to state that text-book descriptions of depression are "stereotyped accounts which have been copied from book to book and repeated from generation to generation" (Grinker, Miller, Sabskin, Munn and Nunnally 1961).

In a very detailed study of sixty-one patients with depressive states, Lewis (1934b) assembled numerous psychiatric opinions which his clinical observations tended to support or refute. His study was carried out before effective treatment for depression was available and his approach, being primarily descriptive and interpretive, paid little attention to quantifying the severity of individual depressive symptoms. Such quantification has only become possible since suitable rating scales have become available, many of them constructed to measure the changes produced by effective antidepressant therapy. Some of the scales currently used in rating depression have been reviewed by Cutler and Kurland (1961). Hamilton's scale, in the author's

opinion one of the most suitable instruments for clinical research, provided detailed information regarding the symptoms of depression and the degree with which they fluctuated with age and severity of illness. This information, together with the findings yielded by the factor analysis, can be considered in the light of two investigations carried out by Foulds and Caine (1959) and Foulds (1960).

It is interesting to note that on the Hamilton scale the severity of five depressive symptoms varied significantly with age, one decreasing and four rising in older patients. The decline in the severity of genital symptoms with advancing age registered by the scale was reflected in the changes taking place with age in the scores on factor 4, and is comprehensible in the light of everyday experience. Similarly a moment's reflection persuades that the common sleep disturbance of the elderly is terminal insomnia, in contrast to the initial insomnia from which younger individuals suffer; the increase in terminal insomnia in the older depressives is therefore not wholly unexpected. Foulds (1960) too found that terminal insomnia was commoner in psychotic depressives over 60 than those under 60, but concluded that sleep disturbance was associated with age rather than psychotic depression. In the present study, agitation also increased significantly with increasing age; Foulds could distinguish between psychotic and neurotic depressives by means of this symptom, but found it to be present in psychotic depressives both over and under 60 years of age. Nevertheless clinical experience suggests that agitation is commoner in older patients - indeed this symptom is one of the hallmarks of "involutional melancholia" - so that to find it increasing in severity with increasing age was not surprising. The finding was born out by the factor analysis, an increase in the scores in

factor 1 "anxiety-agitation" being noted to occur with increasing age as well as a decrease in scores on factor 4. In regard to the increase that took place with age in depressed mood and loss of insight, it is conceivable that older depressives with less to look forward to than their younger counterparts, might become gloomier and, being in general in poorer physical condition, might lose more weight than younger patients. It must be admitted, however, that these are makeshift explanations and provide no answer as to why the overall severity of depression, as registered by the Hamilton scale, did not rise with age. Decline in severity in genital symptoms would not be likely to completely counterbalance the increase in the other four symptoms and again if such explanations are true, why do not other symptoms also increase in severity with increasing longevity?

In terms of overall increase in severity, the significantly greater increase shown by the scale in the severity of agitation, guilt, suicidal proclivities, loss of insight and hypochondriasis was an unexpected finding. With the exception of loss of insight, all these symptoms were present in factor 1, the scores of which were affected by severity as well as age. Agitation is interesting in that according to the scale it increased with age as well as severity. Guilt appeared in three of the few factors obtained, rivalled in its high saturations only by agitation which also appeared in three factors. Using guilt as a criterion, Foulds and Caine (1959), by abstracting seven (mainly delusional) items from the MMPI, constructed a Guilt Scale with which they could distinguish between endogenous and reactive depressives. Factor 3, which contained high saturations of guilt, loss of insight and suicidal proclivities also differentiated between endogenous and reactive depressives, those who were endogenously depressed

and/or deluded tending to have the highest scores.

The constellation of symptoms that increased in severity with increase in overall severity is reminiscent of "involutional melancholia". Agitation dominates the symptomatology of this syndrome which is characterized by depression without retardation, anxiety, ideas of unreality, and hypochondriasis (Henderson and Batchelor 1962). Does involutional melancholia exist as a clinical entity? In regard to the fact that this syndrome is generally regarded as the most serious type of depressive illness, it is interesting to note that of the three sub-groups of severely depressed females studied, the middle-aged clinically-severe patients i.e. women aged between 50 and 59 with severe depressions, had the highest Hamilton scale scores. The group means were: middle aged clinically-severe, 75.26; elderly clinically-severe, 62.53; and young clinically-severe, 53.69. Since the middle-aged clinically severe group appeared likeliest to demonstrate the existence of involutional melancholia as a clinical entity, the percentage of patients with no previous history of affective disorder and unequivocal depressive delusions - two criteria commonly employed in making the diagnosis of involutional melancholia - were examined. Of 23 middle-aged clinically-severe patients 15 (65%) had no previous history of psychiatric illness, practically the same proportion as 12 (65%) of 19 elderly clinically-severe cases; of 23 young clinically-severe patients 16 (70%) had had no previous psychiatric illnesses. Of 23 middle-aged clinically-severe patients 5 (22%) were deluded, a lower proportion than 9 (47%) of 19 who were deluded in the elderly clinically-severe group; of 23 young clinically-severe patients 5 (22%) were deluded.

Since the middle-aged clinically-severe patients could not be differentiated from the other groups with the aid of two of the principal criteria used in making the diagnosis of involutional melancholia, the present findings agree with those of Tait, Harper and McClatchey (1957) who similarly found little evidence for the existence of the disorder as a separate entity. From the point of view of the clinical picture, the most typical "involutional melancholics" included in the present investigation generally belonged to the elderly clinically-severe group. Within this group especially, the findings of the Hamilton scale and the factor analysis suggest that the marked increase in agitation, somatic anxiety, psychic anxiety, guilt, hypochondriasis and suicide (factor 1), which occur in consequence of advanced age and a severe degree of illness, can dominate the symptomatology by overshadowing the smaller increase in depressed mood, reduction of work and interests, retardation and general somatic symptoms (factor 2). In old severely depressed patients an increase in guilt (factors 1, 2 and 3) and loss of insight (factor 3) may be associated with delusions and suicide (factors 2 and 3). It seems, therefore, that the clinical syndrome of involutional melancholia in women can be understood in terms of the accentuation of certain symptoms that customarily occurs in older more severely-ill patients. This formulation reconciles a number of familiar clinical observations but does not explain why selective increase in symptom severity with age and increasing severity takes place.

THE CURRENT TREATMENT OF SEVERE DEPRESSIVE STATES

Finally, it is necessary to re-examine the place of electroconvulsive therapy and imipramine in severe depressive states. The role of amitriptyline can then be considered in perspective.

ELECTROCONVULSIVE THERAPY

The review of electroconvulsive therapy provided in chapter 1 demonstrates that this treatment, whilst rapid, safe and effective, carries the disadvantage of an appreciable rate of relapse - 20 to 30 per cent in most studies, manifesting during the six months following cessation of treatment. Nevertheless despite the steadily accruing evidence that antidepressant drugs are also effective and, in particular, can lessen rates of relapse, a proportion of physicians continue to hold that ECT is the treatment of choice for depressive disorders. Such a viewpoint is represented by Cammer (1961) who, comparing ECT favourably with drugs, stresses the effectiveness and speed of action of ECT without mentioning any antidepressant drug by name. Cammer asserts that antidepressants, when unsuccessful, can increase depression, render it refractary to ECT, make additional ECT necessary and convert an acute relatively manageable depression into a chronic state with a poorer prognosis. Cammer's article stimulated Cahagan (1962) to write of "..... an unusual development in psychiatric treatment, that is, the partial replacement of a highly effective and safe mode of treatment (ECT) with an inferior mode (Antidepressive drugs) ....."Cahagan continues "..... it is hard .....to imagine anything more deplorable than the failure to use early and adequate ECT in involutional depression ..... even the most optimistic claims for the 'anti-depressive' drugs are short of the attainments of ECT in the treatment of involutional and other severe depressions..."

The findings of one investigation appear, at first sight, to support this view. Norris and Clancy (1961), comparing drugs and electrotherapy in a series of hospitalized psychotic in-patients, obtained a 19 per

cent response to drugs in 21 patients versus a 90 per cent response to ECT in 22 ($p < .001$). The former group spent an average of 47 days in hospital versus the latter's 38.5 days. In a follow-up averaging nine months per patient, relapse occurred in two of the four patients who had responded to drugs and nine of the 19 patients responding to ECT; but since three and 16 were improved at the time of follow-up, 75 per cent of the drug-treated patients and 84 per cent of those treated with ECT were found to be well. Norris and Clancy believe that the objections usually voiced against ECT apply more to outpatients than inpatients; and they conclude from their results that, in hospitalized depressives, electrotherapy is the treatment of choice. They categorically state: "Electrotherapy has developed into a treatment whose effectiveness and rapidity of action and safety is yet to be challenged by any other method. Its careful use is accompanied by the lowest incidence of complications of any other treatment. It allows the patient to return to his community and to his life as quickly as possible. The judicious use of antidepressant drugs routinely in a hospital situation awaits the development of a drug with much more rapid action and/or one whose results are much more reliable and predictable."

How are these views to be reconciled with impressions that the use of ECT in hospitalized psychotic depressives has markedly decreased since 1958 - from 71 per cent to 33 per cent in one short-term unit in Chicago (Gulevich, Daniels and Margolis 1961), that antidepressives are "the pith of affective therapy" (Saunders 1961) and that drugs can in the future be expected to play a more important part in the treatment of depression. (Mayer Gross, Slater and Roth 1960)?

Cammer ignores the problem of post ECT relapse and his criticism in regard to antidepressants would carry more weight if drugs, dosages and periods of administration were specified in his article. It is difficult to accept that antidepressants significantly worsen depression or necessitate additional ECT without more evidence than Cammer has produced. Cahagan's letter is indicative of a formerly rather widespread attitude which, in most psychiatrists, is now gradually changing as a result of the mounting evidence that many antidepressant drugs are very effective. Norris and Clancy, like Cammer, do not mention the names or the dosages of the drugs they used and quote percentages obtained from results in unduly small numbers of patients, especially in their follow-up. Their contention that white blood counts and liver function tests are necessary accompaniments of antidepressant therapy is not true for newer thymoleptics such as imipramine and amitriptyline. Finally their three week period of drug administration could, with advantage, have been rather longer. In the circumstances it must be concluded that the criticisms of drug treatment that have been cited are not justified by the available evidence, particularly in regard to newer antidepressant compounds such as imipramine and amitriptyline.

IMIPRAMINE

The effectiveness of imipramine in the treatment of depression has been convincingly demonstrated in the investigations described earlier. The 54 per cent rate of response obtained in the present trial, together with the 13 per cent rate of relapse during a follow-up period of six months, is not out of keeping with the results of other studies. Two studies not previously referred to are of particular interest in connection with the present investigation. In the first of these Fleminger and Groden

(1962) correlated the clinical features of depression in 56 patients with their response to imipramine. They found that pronounced individual features were not useful guides to the outcome of treatment with the drug and concluded that factors relating reliably to the response to imipramine required pursuing beyond merely clinical observation. Kiloh, Ball and Garside (1962) investigated 97 patients treated with imipramine by means of a discriminant function analysis, obtaining weighting coefficients which discriminated between responders and non-responders. Age over 40, a qualitative difference in the subjective experience of depression from "normal depression", weight loss greater than 7 lb., an insidious onset, a duration of under one year and early waking were positively correlated with a good outcome. The presence of precipitants, a more intense depression, self pity, subjective retardation, a history of a suicidal attempt, irritability, failure of concentration, hypochondriasis and restless sleep were negatively correlated with a good outcome.

The findings of the present investigation agree to some extent with those of Kiloh, Ball and Garside and both studies refute the contention of Fleminger and Groden. When Kiloh et al's list of favourable clinical features is examined, it seems that the correlation the author has shown to exist between age and type of depression would make comprehensible the different subjective experience afforded by an old patient with an endogenous depression; loss of weight and terminal insomnia have likewise been demonstrated to be significantly more marked in older depressives. Amongst Kiloh et al's unfavourable features, severity as denoted by "a more intense depression", was found in the present study also, to be associated with a significantly poorer outcome with imipramine. In addition severe symptoms

of depressed mood, reduction of work and interests, retardation, agitation and psychic anxiety, as well as the symptom complex found in factor 2 were all associated with a significantly poorer outcome.

A further point worth noting is the extent to which the inclusion of deluded patients alters the rate of response to imipramine. Evidently the higher the proportion of deluded patients, the lower is the rate of response to this drug. Thus, administering imipramine, Ball and Kiloh (1959) obtained a rate of response of 74 per cent in out-patients with endogenous depressions, few of whom were sufficiently depressed to have delusions of guilt or ideas of self reproach. In the present study, though 73 per cent of non-deluded patients responded, the overall rate of response was only 54 per cent. Friedman, Mowbray and Hamilton (1961) had a similar experience; amongst their sample of in-patient depressives, eight, the most severe, were deluded and none of these responded to imipramine. Accordingly it would appear that the low rates of response obtained in other studies carried out on imipramine in very severe depressives are attributable in part to the inclusion of deluded patients.

Imipramine has been shown to have a stimulant effect and to be capable of activating the psychotic process in schizophrenic patients and non-schizophrenic psychotics (Gershon, Holmberg, Mattson, Mattson and Marshall 1962). Although the upsurge of anxiety related to the withdrawal of imipramine may respond to a resumption of treatment with this drug (Kramer, Klein and Fink 1961), imipramine has generally been believed to increase agitation and anxiety. Mania following imipramine (Ball and Kiloh 1959) and imipramine combined with electroconvulsive treatment (Jotkowitz and Gershon 1962) has also been reported. The findings of the present trial

provide no evidence that imipramine leads to an increase in agitation, although the presence of marked agitation was associated with a significantly poorer prognosis. The "increased" agitation shown on occasions by old severely ill patients is probably related to imipramine's relative inefficiency in such cases and may be a release effect produced by the amelioration of other symptoms.

As mentioned earlier, side effects were not a problem with imipramine either in the in - or the out-patient phase. The detailed ratings carried out in the first sixty patients demonstrated that many "side effects" were actually concomitants of depression rather than products of the two drugs. Busfield, Schneller and Capra (1962), who found it possible to distinguish between "false" and "true" side effects with antidepressants, reached the same conclusion. One patient in the group on imipramine developed retention of urine which cleared when the drug was discontinued; parenthetically this "true" side effect can be of value in the treatment of enuresis (MacLean 1960). In general, however, side effects with imipramine were trivial; apart from one case of glaucoma produced by amitriptyline, they were indistinguishable from those evoked by the latter drug.

Finally it is noteworthy that four of the five patients who died during the trial were in the group on imipramine. Two patients died during the in-patient phase of the trial. The mode of death of the first patient, who after twenty days of imipramine ingestion developed a confusional state with anxiety, restlessness, coarse involuntary movements and hyperpyrexia, resembled that described in other cases of imipramine overdosage (Lancaster and Foster 1959, Lee 1961). The second, a 69 year old hypertensive who died in her sleep on the fourth day of imipramine administration, was not

attributed to the drug. Nevertheless the suggestion has been made by Kristiansen (1961) that imipramine can affect the heart adversely in older patients, especially if heart disease is already present. On the basis of experimental work in animals, Cairncross and Gershon (1962) have postulated that the anticholinergic effect of imipramine may increase heart rate with a resulting decrease in stroke volume and an unaltered cardiac output. This could lead, they think, to hypotensive episodes, relative circulatory stasis and venous pooling i.e. a condition resembling congestive failure could be produced, which in turn could lead to myocardial infarction or the precipitation of cardiac failure. Cairncross and Gershon believe that chronic imipramine medication should be carefully controlled in patients with atherosclerosis, essential hypertension or a previous history of cardio-vascular disease; further, although imipramine is well tolerated in patients with normal cardio-vascular function, any excessive exertion which puts an undue load on the heart may, they think, induce cardiac impairment. On the other hand, the demise of the third patient who, during the follow up, was suspected of having a malabsorption syndrome, was probably due to suicide during a relapse whilst on imipramine. A fourth patient who had had no imipramine for two months, committed suicide soon after absconding from the mental hospital to which she had been admitted in relapse.

AMITRIPTYLINE

According to Denber, Rajotte and Ross (1960), to be regarded as effective, a new antidepressant compound should (1) produce remission in a period of time similar to the one required in known documented treatments (i.e. ECT); (2) produce remission in 80 per cent or more patients in a double-blind study which can be reduplicated by others using similar case material;

(3) break up the cyclic swings of the depressive disorder and above all, through maintained medication prevent their reappearance. Amitriptyline, in the present study, produced remission when successful in practically the same period of time as that required by ECT (median stay in hospital for amitriptyline 37 days, median stay for ECT 34 days); remission was produced in 81 per cent of 69 hospitalized female depressives under double-blind conditions; and a six-month follow up of 46 responders who continued to take amitriptyline revealed a 9 per cent rate of relapse. Accordingly it is apparent that amitriptyline satisfies Denber et al's criteria of effectiveness, though the findings require replication and the role of amitriptyline in male depressives and depressed out-patients requires further investigation.

Three studies comparing amitriptyline and imipramine are of interest in connection with the results obtained in the present investigation. Oltman and Friedman (1961), in a blind study, found that 72 per cent of 50 female depressives treated with amitriptyline responded in contrast to 71 per cent of 80 patients given imipramine. Ayd (1960) obtained a 79 per cent response to amitriptyline in 130 patients; 73 per cent of 100 patients responded to imipramine. Weiss and Pressman (1961), who treated 100 ambulatory patients with amitriptyline and 100 with imipramine, obtained response rates of 79 and 75 per cent respectively.

The present findings in regard to amitriptyline correspond closely with those of Ayd and Weiss and Pressman, and are not markedly different from those of Oltman and Friedman. In regard to imipramine, however, they differ rather strikingly. In this connection Fox (1961) has pertinently observed that apparently contradictory findings resulting from studies which are not strictly comparable need not be regarded as being dis-

crepant but can be regarded as "the outcome of a constellation of therapeutic effects". In both Ayd's and Weiss and Pressman's sample, a number of patients not suffering from pure depressive syndromes were included, and Ayd mentions combining amitriptyline with ECT and tranquillisers on some occasions. In regard to the patients who received imipramine in the present investigation, mention has already been made of the high proportion who were unequivocally deluded (17 of 68 : 25%). Since no deluded patient on imipramine responded, the overall response was rather low (54%). In the amitriptyline group, on the other hand, a smaller proportion were deluded (10 of 69 : 13%). However four of the ten deluded patients in this group responded, and amitriptyline was also superior to imipramine in non-deluded cases (88% versus 73%). It is clear, therefore, that the unequal numbers of deluded patients on the two drug groups, whilst affecting the results, did not invalidate the general findings in favour of amitriptyline.

One patient who responded to amitriptyline died during the period of follow up, as has already been described. Although early in the trial acute retention of urine in one patient caused some inconvenience, the only serious side effect was a case of glaucoma which occurred the day after discharge and necessitated an immediate operation. There was no evidence, despite the claims that have been made, that the side effects of amitriptyline were less troublesome than those produced by imipramine. With both drugs, both in the in-patient and the out-patient phases of the trial, side effects were trivial and of little consequence. Ayd (1961) and Weiss and Pressman (1961) mention fairly numerous, though subjectively mild, side effects with amitriptyline; it may be that the drug, given in full doses in out-patients, produces fewer side effects than imipramine. This could not be

verified in the present study since only in-patients received full doses and, when followed up as out-patients, were placed on lower (maintenance) levels. On the other hand, from the concomitant use of amitriptyline in patients not included in the trial, an impression was gained that in the elderly and frail, amitriptyline, like imipramine, should be used in low doses. In some of these patients weakness, giddiness and tremor observed with both drugs which, like the associated confusion, cleared when they were discontinued.

With the exception of the young clinically-severe group in which the two drugs were equivalent, amitriptyline was found to be more effective than imipramine in every group of patients included in the investigation. Reference has already been made to the superiority of amitriptyline in deluded patients; it was also more effective than imipramine in relieving patients with severe degrees of twelve of the seventeen symptoms on Hamilton's scale and in relieving those with positive scores on factors 1 and 2 (anxiety-agitation and retarded depression). Again amitriptyline was significantly superior to imipramine in older patients, those who were postmenopausal, those who were severely ill and those suffering from endogenous depressions. In retrospect, the outcome with amitriptyline could probably have been estimated from the first-week response to treatment, particularly in patients over 50 years of age with severe depressions and in those over 60; failure to improve in the first week in middle insomnia, gastro-intestinal somatic symptoms and reduction in work and interests was significantly associated with failure to response. In those who did respond, appreciable improvement usually occurred within a week in fifteen of the seventeen symptoms on Hamilton's scale. The decrease in suicidal tendencies, psychic anxiety, somatic anxiety, reduction of work and interests, agitation, gastro-intestinal somatic symptoms, initial

insomnia and middle insomnia was appreciable. The tranquillizing effect of amitriptyline together with the effect it exerted on appetite and sleep suggests that, when successful, the drug may rectify the functional hypothalamic shift which, according to Pollitt (1961), underlies depressive illness.

The findings must finally be evaluated in relationship to other treatments for depression. Amitriptyline was highly effective in a high proportion of the depressive women to whom it was given. This high level of effectiveness was associated with rapid amelioration of most of the symptoms of depression and a generally high level of safety. Within limits, response was predictable and continued maintenance therapy, as advocated by Ayd (1960, 1961c), was associated with a low rate of relapse. Against amitriptyline, imipramine compared unfavourably and iproniazid, according to Cole Jones and Klerman (1961) the standard of evaluation for the monoamine oxidase inhibitors, on published reports, emerges less favourably still. Although the present findings are based on a homogeneous sample of hospitalized female depressives, they appear sufficiently clear-cut to render amitriptyline the treatment of choice for the majority of patients with depressive states.

SUMMARY

The findings are discussed in regard to the phenomenology of depression and the current treatment of severe depressive states.

Some reasons why particular depressive symptoms vary with age and overall severity of illness are advanced. Though the "middle-aged" clinically-severe group of patients was the most severely ill, and therefore

might have been expected to contain a large proportion of involutional melancholics, it could not be distinguished from the "young" or the "elderly" groups in respect of either lack of a previous history or the presence of depressive delusions. This suggests that involutional melancholia, at least in the form in which it is usually described, is not a clinical entity; the characteristic symptom-profile of this condition is to be ascribed, it is thought, to the increase in the severity of particular symptoms which customarily occurs in older patients with severe depressive illnesses.

The current treatment of severe depressive states comprises electroconvulsive therapy, imipramine or amitriptyline. Though electroconvulsive therapy is rapid, safe and effective, the high rate of relapse following treatment is a serious disadvantage. The tendency to relapse after ECT is disregarded by some of its advocates who, comparing it with antidepressants sometimes do not provide the names, doses or durations of treatment of the drugs they have administered. Imipramine, prior to amitriptyline the most effective antidepressant, is not of much value in severe depression and deluded patients seldom, if ever, respond. Apart from these, outcome is difficult to predict when imipramine is given, and cardiac toxicity is a potential hazard. Amongst patients who, responding to imipramine, are kept on maintenance medication, the rate of relapse is fairly low. Amitriptyline has usually produced high response rates in earlier studies and the findings of the present investigation do not differ from these. The drug is more effective than imipramine in severe depressives and, unlike the older compound, produces a remission in a proportion of deluded patients. Outcome can be predicted, within limits, from the first-week response to

treatment. Amitriptyline appears to have few serious side effects and continued administration is associated with a low rate of relapse. The present findings in regard to amitriptyline - an 81 per cent response in 69 hospitalized female depressives with a 9 per cent rate of relapse amongst 46 responders kept on maintenance dosage for six months - reveal that the compound is more effective than other drugs in the treatment of depression. Though slightly less effective than ECT initially, amitriptyline produces results at six months that are equally good, making it the treatment of choice for the majority of patients with depressive states.

APPENDIX 1.

PSYCHIATRIC BACKGROUND

Patient's Name (Please print) _____ Code Number _____
Surname Christian Names

Date _____ Rater _____

1. Previous hospitalizations for mental illness. Do not regard a transfer between two hospitals as two separate hospitalizations. (Circle one)

   1. No previous hospitalization
   2. Once before
   3. Two or three times before
   4. Four or five times before.
   5. More than five times before.

2. Number of years since mental condition first required medical attention _____

3. Was patient treated with antidepressant drugs or ECT before admission.

   Yes.

   No.

   If patient was treated with drugs or ECT prior to admission, fill in the following:

Treatment	When started	How long given	Effect	Side effects, and Remarks

4. Onset of current illness (Circle one)
   1. Very sudden - developed overnight or over a period of less than 7 days.
   2. Fairly sudden - developed over a period of 1 - 8 weeks
   3. Fairly insidious - developed over a period of 2 months to 2 years.
   4. Very insidious - developed over a period of 2 yrs to 5 yrs.
   5. Unknown.

5. Precipitant of this attack: State None or specify

   Psychological

   Physical

APPENDIX 2.

SOCIAL BACKGROUND OF THE PATIENT

Patient's name: .....Code No. .....
(Surname) (Christian names)

Date _____ Rater _____

1. Patient born: (Circle one)
   1. in Australia
   2. outside Australia: If "yes", in what country? .....
2. Age ..... yrs.
3. Marital status: (circle one)
   1. Single
   2. Divorced
   3. Separated
   4. Widowed
   5. Married or common law.
4. Number of Children .....
5. Education: (circle one)
   1. Primary or less than primary.
   2. Secondary unfinished
   3. Secondary finished
   4. Tertiary unfinished
   5. Tertiary finished.
6. Professional and/or vocational qualifications of the patient: (circle one)
   1. None
   2. Unskilled and semi-skilled worker.
   3. Skilled worker
   4. Trade or similar
   5. Commercial and clerical
   6. Technical and semi-professional
   7. Professional.
7. Patient's occupation: (circle one)
   1. home duties only
   2. employee, position held .....
      place of work .....
8. Source of income (circle one)
   1. own work
   2. husband's work
   3. husband's and own work
   4. own or husband's business
   5. pension
   6. independent means
9. Security of income, as patient sees it.
   1. Absolutely reliable
   2. Fairly reliable
   3. Unreliable
   4. Not known.
10. Residence - house, flat, hostel, rooms, other (underline)
    1. owned and paid for
    2. owned and being paid for in instalments
    3. rented.

APPENDIX 3.

PHYSICIAN'S RATING SCALE FOR DEPRESSION*

Pt's Name ..... Date ..... Date Code .....

Hosp. No..... Unit & Ward No..... Pt's Code No.....

Key of Grading of Scores

(0-4) 0: Absent 1: Mild 2: Moderate 3: Severe 4: Very Severe

(0-2) 0: Absent 1: Slight or doubtful 2: Clearly Present

Item No.	Description of Symptoms	Score Range	Raters' Initials.		
1	Depressed Mood	0-4			
2	Retardation	0-4			
3	Work and Interests	0-4			
4	Guilt	0-4			
5	Suicide	0-4			
6	Anxiety, psychic	0-4			
7	Anxiety, somatic	0-4			
8	Hypochondriasis	0-4			
9	Agitation	0-2			
10	Insomnia, initial	0-2			
11	Insomnia, middle	0-2			
12	Insomnia, delayed	0-2			
13	Somatic symptoms, gastrointestinal	0-2			
14	Somatic symptoms, general	0-2			
15	Genital symptoms	0-2			
16	Loss of Weight	0-2			
17	Loss of insight	0-2			
	Totals:	50			

OVERALL RATING
0 = Nil
1 = Mild. depress.
2 = Mod. depress.
3 = Sev. depress.
4 = V. Sev. depress.

* Hamilton, M. "A Rating Scale for Depression", J. Neurol. Neuros. and Psychol. 23:56-62: 1960.

APPENDIX 3a.

CHECK LIST OF SYMPTOMS OF DEPRESSIVE STATES

Item No.	Description of Symptoms	Score Range
1	**Depressed Mood:** Rate on interview behaviour Gloomy attitude, pessimism about the future Feeling of sadness Tendency to weep (if present) Sadness, etc. 1 Occasional weeping 2 Frequent weeping 3 Extreme symptoms 4	0-4
2	**Retardation:** Rate on interview behaviour Slowness of thought, speech and activity Apathy Stupor Slight retardation at interview 1 Obvious retardation at interview 2 Interview difficult 3 Complete stupor (i.e. unrateable) 4	0-4
3	**Work and Interests:** Feelings of incapacity Listlessness, indecision and vacillation Loss of interest in hobbies Decreased social activities Productivity decreased Unable to work Stopped working because of present illness - 4 (Absence from work after treatment or recovery may rate a lower score)	0-4
4	**Guilt:** Self-reproach, feels he has let people down Ideas of guilt Present illness is a punishment Delusions of guilt Hallucinations of guilt.	0-4
5	**Suicide:** Feels life is not worth living Wishes he were dead Suicidal ideas Attempts at suicide If on background of no suicidal tendency score 3, otherwise score 4	0-4
6	**Anxiety, psychic:** Tension and irritability Worrying about minor matters Apprehensive attitude Fears	0-4
7	**Anxiety, somatic:** Gastrointestinal, wind, indigestion Cardiovascular, palpitations, headaches Respiratory, genito-urinary, etc.	0-4
8	**Hypochondriasis:** Self-absorption (bodily) Preoccupation with health Querulous attitude Hypochondriacal delusions	0-4
9	**Agitation:** Rate on interview behaviour Restlessness associated with anxiety	0-2
10	**Insomnia, initial:** Difficulty in falling asleep	0-2

APPENDIX 3b.

CHECK LIST OF SYMPTOMS OF DEPRESSIVE STATES (contd.)

Item No.	Description of Symptoms	Score Range
11	Insomnia, middle: Patient restless and disturbed during the night Waking during the night	0-2
12	Insomnia, delayed: Waking in early hours of the morning and unable to fall asleep again	0-2
13	Somatic Symptoms, Gastrointestinal: Loss of appetite Heavy feelings in abdomen Constipation	0-2
14	Somatic Symptoms, General: Heaviness in limbs, back, or head Diffuse backache Loss of energy and fatiguability	0-2
15	Genital Symptoms: Loss of libido Menstrual disturbances	0-2
16	Loss of Weight	0-2
17	Loss of Insight Loss of insight .. 2 Partial or doubtful loss 1 No loss .. 0 (Insight must be interpreted in terms of patient's understanding and background)	0-2
	TOTAL	50

APPENDIX 4.

OCCUPATIONAL THERAPY RATING SCALE

SCORE SHEET

Patient's Name _____ Age _____ Code No _____

Date Admitted _____ Date Started O. T. _____ Date Discharged _____

Ward and Date _____ Diagnosis _____

Raters Names and Initials _____

Evaluate all items of behaviour during O. T. activities in the light of the patient's background and intelligence. Scores range for each item from 0, which is normal, through mild impairment of task performance, mild symptoms and mild interference with relationships at 1, and moderate disturbance at 2, to severe difficulties at 3. Do not omit to fill in any item, and do not mark any item "Unrateable".

TASK PERFORMANCE			
1. Grasp of Instructions			
2. Attention to Task			
3. Motivation			
4. Patient's grading of own performance			
SUB TOTAL 1.			
SYMPTOMS			
5. Depression			
6. Retardation			
7. Agitation			
8. Physical Complaints			
SUB TOTAL 2.			
RELATIONSHIPS.			
9. Rapport with occupational therapists			
10. Socialization			
11. Overall attitude to O. T.			
SUB TOTAL 3.			
TOTAL			

REMARKS.

.....

.....

.....

.....

.....

.....

APPENDIX 4(a).

CHECK LIST OF OCCUPATIONAL THERAPY SCALE ITEMS

Item No.	Description of Symptoms

TASK PERFORMANCE

1. Grasp of Instructions: Ability to understand the nature of the task set in O. T.
   - 0. Normal - understands quickly.
   - 1. Fair - occasional repetitions and corrections.
   - 2. Poor - constant repetition and corrections.
   - 3. Very poor - unable to understand.

2. Attention to task: Degree to which attention is sustained throughout the task.
   - 0. Good - Complete attention.
   - 1. Fair - Usually attentive.
   - 2. Poor - Attention limited and wandering.
   - 3. Very Poor - Complete inattention.

3. Motivation: Drive towards performance of the task as manifested throughout it.
   - 0. Good - no urging needed.
   - 1. Fair - little urging.
   - 2. Poor - Much urging.
   - 3. Very poor - refuses completely.

4. Patients grading of own performance: Degree of consistancy between patients evaluation of performance and objective performance.
   - 0. Good - Consistent with objective performance.
   - 1. Fair - Somewhat inconsistent with O. P.
   - 2. Poor - Grossly inconsistent with O. P.
   - 3. Very poor - No recognition of quality.

SYMPTOMS.

5. Depression:- Degree of gloom, sadness, pessimism, despair, weeping.
   - 0. No depression.
   - 1. Mild
   - 2. Moderate
   - 3. Severe.

6. Retardation:- Slowness in thought, speech and activities.
   - 0. None
   - 1. Mild
   - 2. Moderate
   - 3. Severe.

7. Agitation:- Motor restlessness associated with anxiety, pacing, wringing hands, etc.
   - 0. None
   - 1. Mild
   - 2. Moderate
   - 3. Severe

8. Physical complaints:- Physical or mental protestations of unease, distress and disease.
   - 0. None
   - 1. Mild
   - 2. Moderate
   - 3. Severe.

RELATIONSHIPS.

9. Rapport with occupational therapist - degree of empathy with occupational therapist.
   - 0. Good - Friendly, easy accord. Reserved.
   - 1. Fair - Reserved.
   - 2. Poor - Strained, infrequent accord.
   - 3. Very poor - No interpersonal contact.

10. Socialization:- How well patient mixes with other patients.
    - 0. Good - Friendly, easy accord.
    - 1. Fair - Reserved.
    - 2. Poor - Strained infrequent accord.
    - 3. Very poor - No interpersonal contact.

APPENDIX 5.

SIDE EFFECTS RECORD

Patient ..... Physician .....

Number ..... Nurse .....

S = Spontaneous. Score Code: 0 = Absent. 1 = Mild. 2 = Mod. 3 = Sev. 4 = Ext Sev.

WEEK OF STUDY		1			2			3			4			5			6			TOTAL
Day Rated	0	M	W	F	M	W	F	M	W	F	M	W	F	M	W	F	M	W	F	
No. of Capsules																				
1. Clouding																				
2. Dysmnesia																				
3. Agitation Psychic Motor																				
4. Hypomania																				
5. Hallucins. - A V																				
6. Paraesthes. - P V																				
7. Parkinsonian Symptoms																				
8. Pupils : Size Nystagmus Diplopia Accommodation Eyeball Tens.																				
9. Ataxia																				
10. Headache																				
11. Faintness Dizziness Blood Press.↓																				
12. Heartburn Nausea Vomiting Diarrhoea																				
13. Jaundice.																				
14. Micturition Dysuria - Oliguria																				
15. Skin:Flushing - Pruritus Rash																				
16. Sweating Palpitation Tachycardia Dry Mouth Thirst																				
17. Tremor (non Park)																				
18. Muscle:Twitch Fits																				
19. Somnolence																				
20. Other																				

REFERENCES

1. AFFLECK, J.W., FORREST, A.D. and MARTIN, F.M. (1961) "Adjunctive therapy in depression: a controlled trial of nialamide" J. Ment. Sc. 107:997-999.

2. ALEXANDER, L. (1958) Objective approaches to treatment in psychiatry. Springfield: Thomas.

3. _____ (1961a) "Objective evaluation of antidepressant therapy by conditional reflex technique" Dis. Nerv. Syst. 22:14-23, supp.

4. _____ (1961b) "Effects of psychotropic drugs on conditional responses in man" pp 93-123 in Neuro-Psychopharmacology (Edited by E. Rothlin). Amsterdam: Elsevier.

5. APPEL, K.E., MYERS, J.M. and SCHEFLEN, A.E. (1953) "Prognosis in Psychiatry" Arch. Neurol. and Psychiat. 70:459-468.

6. ARGST, J. (1961) "A clinical analysis of the effects of Tofranil in depression" Psychopharmacologia 2:381-407.

7. ANNOTATION (1961) "Suicide notes" Brit.M.J. 1:1667.

8. ANNOTATION (1962) "Suicide and social decline" Brit. M. J. 1:1194-1195.

9. ARMITAGE, P. (1960) Sequential Medical Trials. Oxford: Blackwell.

10. ASHBY, W.R. and COLLINS, G.H. (1961) "A clinical trial of imipramine (Tofranil) on depressed patients" J. Ment. Sc. 107:547-551.

11. AYD, F.J. Jr. (1960) "Amitriptyline (Elavil) therapy for depressive reactions" Psychosomatics 1:1-6.

12. _____ (1961a) Recognizing the depressed patient. New York: Grune and Stratton.

13. _____ (1961b) "Toxic somatic and psychopathologic reactions to antidepressants" J. Neuropsychiat. 2:119-122, supp.

14. _____ (1961c) "A critique of antidepressants" Dis. Nerv. Syst. 22:32-36, supp.

15. _____(1962) "Suicide, a hazard in depression" J. Neuropsychiat. 2:52-54, supp.

16. BALL, J.R.B. and KILOH, L.J. (1959) "A controlled trial of imipramine in the treatment of depressive states" Brit. M. J. 2:1052-1055.

17. BARKER, J.C. and BAKER, A.A. (1959) "Deaths associated with electroplexy" J. Ment. Sc. 105:339-348.

18. BARSA, J.A. and SAUNDERS, J.C. (1961) "Amitriptyline (Elavil), a new antidepressant" Am. J. Psychiat. 117:739-740.

19. BARTHOLOMEW, A.A. (1962) "An evaluation of tranylcypromine (Parnate) in the treatment of depression" M.J. Australia, 655-662.

20. _____ and HARLEY, E. (1959) "Toxic response to 2-phenyl - 3-methyl tetrahydro-1, 4-oxazine hydrochloride ("Preludin") in humans" Psychopharmacologia 1:124-139.

21. BATCHELOR, I.R.C. and NAPIER, M.B. (1953) "Attempted suicide in old age" Brit. M. J. 2:1186-1190.

22. BATES, T.J.N. and DOUGLAS, A.D.McL. (1961) "A comparative trial of four monoamine oxidase inhibitors in chronic depressives" J. Ment. Sc. 107:538-546.

23. BATT, J.C. (1943) "One hundred depressive psychoses treated with electrically induced convulsions" J. Ment. Sc. 89:289-296.

24. BEER, D.T. and SCHAFFNER, F. (1959) "Fatal jaundice after administration of beta-phenylisoprophylhydrazine" J.A.M.A. 171:887-889.

25. BELL, D.S. and THETHOWAN, W.H. (1961) "Amphetamine addiction" J. Nerv. Ment. Dis. 133:489-496.

26. BENNET, D. (1961a) "Treatment of antidepressant states with amitriptyline" Dis. Nerv. Syst. 22:55-56, supp.

27. _____ (1961b) Letter "Amitriptyline in depression" Lancet 1:1287-1288.

28. BIGELOW, N. (1959) "The involutional psychoses" pp 540-545 in American Handbook of Psychiatry (Edited by S. Arieto), New York: Basic Books.

29. BROOK, C.P.B. and STAFFORD-CLARK, D. (1961) "Psychiatric treatment in general wards" Lancet 1:1159-1162.

30. BRUCE, E.M., CRONE, M., FITZPATRICK, G., FREWIN, S.J., GILLIS, A., LASCELLES, C.F., LEVINE, L.J. and MERSKEY, H. (1961) "A comparative trial of ECT and Tofranil" Am. J.Psychiat. 117:76.

31. BURT, C.G., GORDON, W.F., HOLT, N.F. and HOWDERN, A. (1962) "Amitriptyline in depressive states : a controlled trial" J. Ment. Sc. 108:711-730.

32. BURTON, R. (1813) The Anatomy of Melancholy, Volume 2. London: Walker.

33. CADE, J.F.J. and KRUPINSKI, J. (1961) "Incidence of psychiatric disorders in Victoria in relation to country of birth" M. J. Australia, 400-404.

34. CAIRNCROSS, K.D., GERSHON, S. and [illegible], I.D. (1961) "Some aspects of the mode of action of imipramine" J. Neurol. Neurosurg. Psychiat. In press.

35. _____ and _____ "A pharmacological basis for the cardio-vascular complications of imipramine medication" M. J. Australia, 372-375.

36. CAMMER, L. (1961) "Treatment methods and fashions in treatment" Am. J. Psychiat. 118:447.

37. CAPOONE, H.S. and NIXON, J.W.G. (1961) "Short stay psychiatric unit in a general hospital" Lancet 2:1351-1352.

38. CAPSTICK, A. (1960) "Recognition of emotional disturbance and the prevention of suicide" Brit. M. J. 1:1179-1182.

39. CARES, R.M. and BUCKMAN, C. (1961) "A survey of side effects and/or toxicity of newer psychopharmacologic agents" Dis. Nerv. Syst. 22:97-106, supp.

40. CARSTAIRS, G.M. (1960) "Characteristics of the suicide prone" Proc. Roy. Soc. Med. 54:262-264.

41. COLE, C.E., PATTERSON, E.M., CRAIG, J.B., THOMAS, W.E., KISTINE, L.P., STAHLY, M. and PASAMANICK, B. (1959) "A controlled study of the efficacy of iproniasid in the treatment of depression" Arch. Gen. Psychiat. 1:513-518.

42. COLE, J.O., JONES, R.T. and KLERMAN, G.L. (1961) "Drug therapy" pp 539-574 in Progress in Neurology and Psychiatry. Volume XVI (edited by E.A. Spiegel), New York: Grune and Stratton.

43. CONNELL, P.H. (1958) Amphetamine psychoses. London: Chapman and Hall.

44. CRANE, G.E. (1957) "Iproniazid (Marsilid) phosphate a therapeutic agent for mental disorders and debilitating disease" pp 142-152 in Psychiatric Research Reports No.8, Washington D.C.: American Psychiatric Association.

45. CRISP, A.H., HAYS, P. and CARTER, A. (1961) "Three amine-oxidase inhibitor drugs in the treatment of depression" Lancet 1:17-18.

46. CULPAN, R. and DAVIES, B. (1960) "Psychiatric illness at a medical and a surgical outpatient clinic" Comprehen. Psychiat. 1:228-235.

47. CULPEPER, N. (1953) The complete herbal. Birmingham: Kynoch.

48. CUTLER, R.P. and KUNLAND, H.D. (1961) "Clinical quantification of depressive reactions" Arch. Gen. Psychiat. 5:280-285.

49. DALLY, P.J. (1962) Letter "Fatal reaction associated with tranyl-cypromine and methylamphetamine" Lancet 1:1235.

50. DAVIES, G. (1960) Letter "Side effects of phenelzine" Brit. M. J. 2:1019.

51. DAX, E.C. (1961) "The prevention of suicide" M. J. Australia, 47-49.

52. DELAY, J., LAINE, B. and BUISSON, J.F. (1952) "Note on the action of IMH utilised in the treatment of depressive states" Ann. med.-psychol. 2:689-692.

53. DENKER, H.C.B., RAJOTTE, P. and ROSS, E. (1960) "Some observations on the chemotherapy of depression: results with "Taractan" Comprehen. Psychiat. 1:308-312.

54. DOMINION, J. (1960) "Deanol in depression: a controlled trial" J. Ment. Sc. 106:711-712.

55. DORFMAN, W. (1960) "Clinical experiences with amitriptyline" Psychosomatics 1:153-155.

56. _____ (1961) "Masked depression" Dis. Nerv. Syst. 22:41-45, supp.

57. DORPAT, T.L. and RIPLEY, H.S. (1960) "A study of suicide in the Seattle area" Comprehen. Psychiat. 1:349-359.

58. DOUST, J.W., LEWIS, D.J., MILLER, A., SPROTT, D. and WRIGHT, R.D.L. (1959) "Controlled assessment of antidepressant drugs, including Tofranil" Canad. Psychiat. A. J. (Spec. supp.) 4:190-194.

59. DUNLOP, E. (1961a) "The antidepressant qualities of Elavil" Dis. Nerv. Syst. 22:107-109.

60. _____ (1961b) "The treatment of depression in private practice" Dis. Nerv. Syst. 22:46-49, supp.

61. ELITHORN, A. and SLATER, E. (1956) "Prefrontal leucotomy. Views of patients and their relatives" Brit. M. J. 2:739-742.

62. _____ (1958) "Prefrontal leucotomy and depression" Proc. Roy. Soc. Med. 52:203-206.

63. ESSEN-MOLLER, E. and HAGNELL, O. (1960) "The frequency and risk of depression within a rural population group in Scania" Acta Psychiat. Scand. 37:28-32, supp.

64. FABING, H.D., HAWKINS, J.R. and MOULTON, J.A.L. (1955) "Clinical studies on alpha - (2-piperydyl) benzhydrol hydrochloride, a new antidepressant drug" Am. J. Psychiat. 111:832-836.

65. FELDMAN, P.E., (1961) "Psychotherapy and chemotherapy (amitriptyline) of anergic states" Dis. Nerv. Syst. 22:27-30, supp.

66. FITZGERALD, O.W.S. (1943) "Experiences in the treatment of depressive states by electrically induced convulsions" J. Ment. Sc. 89:73-80.

67. FLEMINGER, J.J. and GRODEN, B.M. (1962) "Clinical features of depression and the response to imipramine (Tofranil)" J. Ment. Sc. 108:101-104.

68. FOULDS, G.A. (1960) "Psychotic depression and age" J. Ment. Sc. 106:1394-1396.

69. _____ and CAINE, T.M. (1959) "The assessment of some symptoms and signs of depression in women" J. Ment. Sc. 105:181-189.

70. FOX, B. (1961) "The investigation of the effects of psychiatric treatment" J. Ment. Sc. 107:493-502.

71. FREED, H. (1960) "On the parenteral use of amitriptyline" Am. J. Psychiat. 117:455-456.

72. FREEMAN, W. (1957) "Frontal lobotomy 1936-1956. A follow up study of 3,000 patients from one to twenty years" Am. J. Psychiat. 113:877-886.

73. FREMMING, K.H. (1947) Morbid risk of mental diseases and other mental abnormalities in an average Danish population. Copenhagen: Munksgaard.

74. FREYHAN, F.A. (1960) "The modern treatment of depressive disorders" Am. J. Psychiat. 116:1057-1064.

75. FRIEDMAN, C., MOWBRAY, M.S. and HAMILTON, V.J. (1961) "Imipramine (Tofranil) in depressive states" J. Ment. Sc. 107:948-953.

76. GERSHON, S., HOLMBERG, G., MATTSSON, E., MATTSON, L. and MARSHALL, A. (1962) "Imipramine hydrochloride" Arch. Gen.Psychiat. 6:112-118.

77. GOLDMAN, D. (1962) "Historical aspects of electro shock therapy, electrical current modifications, treatment techniques and some electroencephalographic observations" J. Neuropsychiat. 3:210-215.

78. GRINKER, R.R., MILLER, J., SABSHIN, M., NUNN, R. and NUNNALLY, J.C. (1961) The Phenomena of Depressions. New York: Hoeber.

79. GULEVICH, G., DANIELS, R.S. and MARGOLIS, P.M. (1961) "The decreasing use of electroconvulsive therapy" Am. J. Psychiat. 118:555-557.

80. HAMILTON, M. (1960) "A rating scale for depression" J. Neurol. Neurosurg. Psychiat. 23:56-62.

81. _____ and WHITE, J.M. (1959) "Clinical syndromes in depressive states" J. Ment. Sc. 105:985-998.

82. _____ and _____ (1960) "Factors related to the outcome of depression treated with ECT" J. Ment. Sc. 106:1031-1041.

83. HANSON, H.M. (1961) "The effects of amitriptyline, imipramine, chlorpromazine and nialamide on avoidance behaviour" Fed. Proc. 20:396.

84. HARE, E.H., DOMINION, J. and SHARPE, I. (1962) "Phenelzine and dextroamphetamine in depressive illness. A comparative trial" Brit. M. J. 1:9-12.

85. HARRIS, A. (1938) "Cardiazol treatment of schizophrenia" J. Ment. Sc. 84:735-775.

86. HARRIS, J.A. and ROBIN, A.A. (1960) "A controlled trial of phenelzine in depressive reactions" J. Ment. Sc. 106:1432-1437.

87. HELGASON, T. (1960) "The frequency of depressive states in Iceland as compared with the other Scandinavian countries" Acta Psychiat. Scand. 37:81-90, supp.

88. HELSBORG, H.C. (1958) "Psychiatric investigations of patients in a medical department" Acta Psychiat. et Neurol. Scand. 33:303-335.

89. HENDERSON, D.K. and BATCHELOR, I.R.C. (1962) Henderson and Gillespie's Textbook of Psychiatry. Ninth Edition. London: Oxford.

90. HEMR, F., STEMART, J. and CHAREST, M.P. (1961) "Tranquilizers and antidepressants: a pharmacological comparison" Biochemical Pharmacology. 8:25-26.

91. HIRSCH, J. (1959) "Suicide" Mental Hygiene 43:516-524.

92. _____ (1960a) "Methods and fashions of suicide" Mental Hygiene 44:3-11.

93. _____ (1960b) "Dynamics of suicide" Mental Hygiene 44:274-290.

94. HOBSON, R.F. (1953) "Prognostic factors in electroconvulsive therapy" J. Neurol. Neurosurg. Psychiat. 16:275-281.

95. HOLT, J.P., WRIGHT, E.R. and HECKER, A.O. (1960) "Comparative clinical experience with four antidepressants" Am. J. Psychiat. 117:533-538.

96. HOUDETH, A. (1955) Unpublished clinical material.

97. _____ (1956) Unpublished clinical material.

98. _____ (1962) "Current concepts in teaching psychiatry to medical undergraduates" M. J. Australia. 1020-1023.

99. _____ and SOMERVILLE, D.M. (1962) "The general practitioner and psychiatric drug treatment" M. J. Australia, 404-411.

100. HOPKINS, P. (1956) "Referrals in general practice" Brit. Med. J. 2:873-877.

101. HUCKER, H.B. and PORTER, C.C. (1961) "Studies on the metabolism of amitriptyline" Fed. Proc. 20:172.

102. HUSTON, P.E. and LOCHER, L.M. (1948a) "Involutional psychosis, course when untreated and when treated with electric shock" Arch. Neurol. and Psychiat. 59:385-394.

103. _____ and _____ (1948b) "Manic-depressive psychosis, course when treated and untreated with electric shock" Arch. Neurol. Psychiat. 60:37-43.

104. HUTCHINSON, J.T. and SMEDBERG, D. (1960) "Phenelzine (Nardil) in the treatment of endogenous depression" J. Ment. Sc. 106:704-710.

105. IMPASTATO, D.J. and BERG, S. (1956) "Methods of administration of succinylcholine dichloride in electroshock therapy with a description of a simple and modified technique and a succinylcholine dichloride test" Am. J. Psychiat. 112:893-897.

106. _____ and GABRIEL, A.R. (1958) "P.M. - G.M. Succinylcholine-modified electroshock therapy without barbiturates" Am. J.Psychiat. 114:698-702.

107. JOSHI, V.G. (1961) "Controlled clinical trial of isocarboxazid (Marplan) in hospital psychiatry" J. Ment. Sc. 107:567-571.

108. JOTKOWITZ, M.W. and GERSHON, S. (1962) "Manic reactions following combined "Tofranil" (imipramine) and electroconvulsive therapy" M. J. Australia, 87-90.

109. KALINOWSKY, L.B. (1954) "Some problems in electroconvulsive therapy of depressions" pp 190-198 in Depression (Edited by P.H. Hoch and J. Zubin). New York: Grune and Stratton.

110. _____ (1959) "Convulsive Shock treatment" pp 1499-1520 in American Handbook of Psychiatry (Edited by S. Ariete), Basic Books, New York: Basic Books.

111. KARACULLA, S. (1950) "Evaluation of electro-convulsive therapy as compared with conservative methods of treatment in depressive states" J. Ment. Sc. 96:1060-1091.

112. KENNEDY, A. (1940) "The treatment of mental disorders by induced convulsions" J. Neurol. Psychiat. 3:49-82.

113. _____ and FISH, F.J. (1959) "Alcoholism, alcoholic addiction and drug addiction" pp 277-302 in Recent Progress in Psychiatry Vol. 3 (Edited by G.W.T.H. Fleming and A. Walk) London: Churchill.

114. KENNING, I.S., RICHARDSON, V.L. and TUCKER, F.G. (1960) "The treatment of depressive states with imipramine hydrochloride" Canad. Psychiat. A.J. 5:60-64.

115. KESSEL, N. and GROSSMAN, G. (1961) "Suicide in alcoholics" Brit. Med. J. 2:1671-1672.

116. KILOH, L.G. and BALL, J.R.B. (1961) "Depression treated with imipramine: a follow-up study" Brit. M. J. 1:168-171.

117. _____, _____, and GARSIDE, R.F. (1962) "Prognostic factors in treatment of depressive states with imipramine" Brit. M. J. 1:1225-1227.

118. _____, and BRANDON, S. (1962) "Habituation and addiction to amphetamines" Brit. M. J. 2:40-43.

119. _____, CHILD, J.P. and LATNER, G. (1960) "A controlled trial of iproniazid in the treatment of endogenous depression" J. Ment. Sc. 106:1139-1144.

120. _____, _____, and _____ (1961) "Endogenous depression treated with iproniazid - A Follow Up Study" J. Ment. Sc. 106:1425-1428.

121. KING, P.D. (1959) "Phenelzine and ECT in the treatment of depressions" Am. J. Psychiat. 116:64-65.

122. KINO, F.F., and THORPE, F.T. (1946) "Electrical convulsion therapy in 500 selected psychotics" J. Ment. Sc. 92:138-145.

123. KLINE, N.S. (1958) "Clinical experience with iproniasid (Marsilid)" J. Clin. Exper. Psychopath. 19:72-78, supp 1.

124. _____, with LOGNER, H.P., and SAUNDERS, J.C. (1957) "A clinical and pharmacodynamic evaluation of iproniasid as a psychic energiser" pp 129-141 in Psychiatric Research Reports No.8. Washington, D.C.: American Psychiatric Association.

125. KOLB, L. and VOGEL, V.H. (1942) "The use of shock therapy in 305 mental hospitals" Am. J. Psychiat. 99:90-100.

126. KRAEPELIN, E. (1921) Manic depressive insanity and paranoia (translated by M. Barclay). Edinburgh: Livingstone.

127. KRAMER, J.C., KLEIN, D.F., and FINK, M. (1961) "Withdrawal symptoms following discontinuation of imipramine therapy" Am. J. Psychiat. 118:549-550.

128. KRISTIANSEN, E.S. (1961) "Cardiac complications during treatment with imipramine (Tofranil)" Acta Psychiat. et Neurol. Scand. 36:427-442.

129. KREUPINSKI, J. and STOLLER, A. (1962) "Survey of Institutionalised Mental Patients in Victoria, Australia, 1882 to 1959" M. J. Australia, 271-276, 314-321 and 359-367.

130. KUHN, R. (1957) "Uber die behandlung depressiver sustande mit einem iminobenzylderivat (G22355)" Schwiez. med. Wschr. 87:1135-1140.

131. _____ (1958) "The treatment of depressive states with G22355 (imipramine hydrochloride)" Am. J. Psychiat. 115:459-464.

132. LANCASTER, N.P. and FOSTER, A.R. (1959) "Suicidal attempt by imipramine overdosage" Brit. Med. J. 2:1458.

133. LARSON, T., and SJOGREN, T. (1954) A methodological, psychiatric and statistical study of a large Swedish rural population. Copenhagen: Munksgaard.

134. LEADING ARTICLE (1961) "Management of attempted suicide" Brit. M. J. 2:1201-1203.

135. LEE, F.I. (1961) "Imipramine overdosage - report of a fatal case" Brit. M. J. 1:338-339.

136. LEHMANN, H.E. (1959) "Psychiatric concepts of depression: Nomenclature and classification" Canad. Psychiat. A. J. (Spec. Supp). 4:1-10.

137. _____, CAHN, C.H. and De VENTUIL, R.L. (1958) "The treatment of depressive conditions with imipramine (G 22355)" Canad. Psychiat. A. J. 3:155-164.

138. LEIGH, D. (1955) "Domiciliary consultation in psychiatric practice" Lancet 2:1285-1287.

139. LEMERE, F. (1953) "What happens to alcoholics" Amer. J. Psychiat. 109:674-676.

140. LEWIS, A.J. (1934a) "Melancholia: a historical review" J. Ment. Sc. 80:1-42.

141. _____ (1934b) "Melancholia: a clinical survey of depressive states" J. Ment. Sc. 80:277-378.

142. _____ (1956) "Affective disorder" pp 1645-1656 in Price's Textbook of the Practice of Medicine". Ninth Edition. Edited by Donald Hunter. London: Oxford.

143. LEYBERG, J.T. and DENMARK, J.C. (1959) "The treatment of depressive states with imipramine hydrochloride (Tofranil)" J. Ment. Sc. 105:1123-1126.

144. LOW, A.A., SOMENTHAL, I.R., BLAUROCK, N.F., KAPLAN, M. and SHERMAN, I. (1938) "Metrazol shock treatment of the 'functional psychoses'" Arch. Neurol. and Psychiat. 39:717-736.

145. MACLEAN, R.E.G. (1960) "Imipramine hydrochloride (Tofranil) and eneurosis" Am. J. Psychiat. 117:551.

146. MARLEY, E. (1959) "Response to drugs and psychiatry" J. Ment. Sc. 105:19-43.

147. MASON, A. (1962) Letter "Fatal reaction associated with tranylcypromine and methylamphetamine" Lancet 1:1073.

148. MAYER GROSS, W. (1954) "The diagnosis of depression" Brit. M. J. 2:948-950.

149. _____, SLATER, E. and ROTH, M. (1960) Clinical psychiatry. Second edition. Cassell, London.

150. McCORMICK, T.C. (1962) "Toxic reactions to the amphetamines" Dis. Nerv. Syst. 23:219-224.

151. MENNINGER, K.A. (1938) Man against himself. New York: Harcourt Brace.

152. MYERSON, A. (1936) Effect of benzedrine sulfate on mood and fatigue in normal and neurotic persons" Arch. Neurol. Psychiat. 36:816-822.

153. NATIONAL ASSOCIATION FOR MENTAL HEALTH (1961) "Everybody's Business" Lancet 1:608-609.

154. NOMURA, A. (1960) "Treatment of depression in relation to suicidal attempts" Dis.Nerv. System. 21:701-703.

155. NORRIS, A.,S. and CLANCY, J. (1961) "Hospitalized depressions" Arch. Gen. Psychiat. 5:276-279.

156. NORRIS, V. (1951) Mental Illness in London. London: Chapman and Hall.

157. OAKLEY, D.P. (1961) "Comparison of two anti-depressant drugs (imipramine and phenipramine) in endogenous depressive illnesses in female in-patients" J. Ment. Sc. 107:1000-1002.

158. ODEGARD, O. (1946) "A statistical investigation of the incidence of mental disorder in Norway" Psychiat. Quart. 20:381.

159. OLMAN, J.E., and FRIEDMAN, S. (1961) "Elavil in the treatment of depressive disorders (and comparison with Tofranil)" Am. J. Psychiat. 118:547-547.

160. O'NEAL, P., ROBINS, E. and SCHMIDT, E.H. (1956) "A psychiatric study of attempted suicide on persons over 60 years of age" Arch. Neurol. & Psychiat. 75:175-284.

161. OSTFELD, A.M. (1961) "Effects of an antidepressant drug on test of mood and perception" Dis. Nerv. Syst. 22:24-56, supp.

162. PAINTRIDGE, M. (1949) "Some reflections on the nature of affective disorders arising from the results of prefrontal leucotomy" J. Ment. Sc. 95:795-825.

163. _____ (1954) "Indications and contraindications for ECT" Postgrad. M. J. 30:176-184.

164. PEOPLES, S.A. and GUTTMAN, E. (1936) "Hypertension produced with benzedrine" Lancet 1:1107-1109.

165. PERRIN, G.M. (1961) "Cardiovascular aspects of electric shock therapy" Acta Psychiat. et Neurol.Scand., supp 152.

166. PIPPARD, J. (1962) "Leucotomy in Britain today" J. Ment. Sc. 108:249-256.

167. PLETSCHER, A. and GEY, K.F. (1961) "Interference with the permeation of aromatic monoamines and amino-acids in brain, a possible new type of drug action" Biochemical Pharmacology 8:82.

168. POLLITT, J.D. (1960) "Depression and the functional shift" Comprehen. Psychiat. 1:381-390.

169. PRESSMAN, M.D. and WEISS, L.B. (1961) "Experience with Elavil: treatment of fifty-one cases of depression" Am. J. Psychiat. 118:74-75.

170. PSYCHOPHARMACOLOGY SERVICE CENTER (1962) "A selective list of drugs used in psychiatry" Psychopharm. Serv. Center Bull. (U.S. Department of Health, Education and Welfare) 2: March.

171. REES, L. (1960) "Treatment of depression by drugs and other means" Nature 186:114-120.

172. _____ and BENAIM, S. (1960) "The evaluation of iproniazid in the treatment of depression" J. Ment. Sc. 106:193-202.

173. _____, BROWN, A.C. and BENAIM, S. (1961) "A controlled trial of imipramine (Tofranil) in the treatment of severe depressive states" J. Ment. Sc. 107:552-559.

174. _____ and DAVIES, B. (1961) "A controlled trial of phenelzine (Nardil) in the treatment of severe depressive illness" J. Ment. Sc. 107:560-566.

175. ROBERTS, J.M. (1959) "Prognostic factors in the electroshock treatment of depressive states" J. Ment. Sc. 105:693-702.

176. ROBIN, A.A., and WISEBERG, S. (1958) "A controlled trial of methylphenidate ('Ritalin') in the treatment of depressive states" J. Neurol. Neurosurg. Psychiat. 21:55-57.

177. ROSENBAUM, M. and GERSHON, S. (1962) "Experiences with a new anti-depressant - amitriptyline" M. J. Australia, 321-325.

178. ROTH, M. (1952) "A theory of ECT action and its bearing on the biological significance of epilepsy" J. Ment. Sc. 98:44-59.

179. _____ (1956) Personal communication.

180. _____ (1959) "The phenomenology of depressive states" Canad. Psychiat. A. J. (Spec. Supp.) 4:32-53.

181. _____ (1960a) "Depressive states and their borderlands: classification, diagnosis and treatment" Comprehen. Psychiat. 1:135-155.

182. _____ (1960b) "The phobic anxiety-depersonalisation syndrome and some general aetiological problems in psychiatry" J. Neuropsychiat. 1:293-306.

183. _____ and GARSIDE, R. (1962) "Some characteristics common to electroconvulsive therapy and prefrontal leucotomy and their bearing on the mode of action of the two treatments" J. Neuropsychiat. 3:221-230.

184. _____ and MORRISSEY, J.D. (1952) "Problems in the diagnosis and classification of mental disorder in old age; with a study of case material" J. Ment. Sc. 98:66-80.

185. _____ and ROSIE, J.M. (1955) "The use of electroplexy in mental disease with clouding of consciousness" J. Ment. Sc. 99:103-111.

186. ROTHMAN, T., GRAYSON, H. and FERGUSON, J. (1961a) "An evaluation of the effectiveness of isocarboxazid (Marplan) in depressive syndromes" Comprehen. Psychiat. 2:27-34.

187. _____, _____ and _____ (1961b) "A comparative investigation of isocarboxazid and imipramine in depressive syndromes" J. Neuropsychiat. 2:158-162.

188. RYLE, A. (1961) "Psychoses in general practice: an epidemiological survey" J. Ment. Sc. 107:1020-1027.

189. SABELLI, H., LEVIN, J., SIEGLER, L. and TOMAN, J. (1961) "Central and peripheral effects of amitriptyline and ethyltryptamine" Pharmacologist (Wash., D.C.) 3:68.

190. SAINSBURY, P. (1960) "Suicide in old age" Proc. Roy. Soc. Med. 54:266-268.

191. SARGANT, W. (1962) "The present indications for leucotomy" Lancet 1:1197-1200.

192. _____ and SLATER, E. (1944) An introduction to physical methods of treatment in Psychiatry. Edinburgh. Livingstone.

193. SAUNDERS, J.C. (1961) "Antidepressives: the pith of affective therapy" Dis. Nerv. Syst. 22:37-40 supp.

194. SCHUFF, B. (1961) "Application de un nouvo farmaco antidepresivo en gastro-criterologie" Din Medico 33:1942-1944.

195. SEAGER, C.P. (1959) "Controlled trial of straight and modified electroplexy" J. Ment. Sc. 105:1022-1028.

196. SETTEL, E. (1961) "Recognition and treatment of depression with amitriptyline" Clin. Med. (Minnetka) 8:1949-1954.

197. SHENTEY, M.J. (1955) "Psychopathology and personality structure in chronic alcoholism" pp 16-42 in Diethelm, O. (1955) Etiology of Chronic Alcoholism, Springfield: Thomas.

198. SIEGEL, S. (1956) Nonparametric statistics. London: McGraw-Hill.

199. SLATER, E. (1951) "Evaluation of electroconvulsive therapy as compared with conservative methods of treatment in depressive states" J. Ment. Sc. 97:567-569.

200. SORENSON, A. and STROMGREN, E. (1960) "Frequency of depressive states within geographically delimited population groups: prevelence (the Samso investigation)" Acta Psychiat. Scand. 37:62-68 supp.

201. STENGEL, E. (1952) "Enquiries into attempted suicide" Proc. Roy. Soc. Med. 45:613-620.

202. _____ (1960a) "Old and new trends in suicide research" Brit. J. Med. Psychol. 33:283-286.

203. _____ (1960b) "The complexity of motivations to suicidal attempts" J. Ment. Sc. 106:1388-1393.

204. STENSTEDT, A. (1952) "A study in manic-depressive psychosis. Clinical, social and genetic investigations" Acta Psychiat. et Neurol. Scand. Suppl. 79, Copenhagen.

205. TAIT, A.C., HARPER, J. and McCLATCHEY, W.T. (1957) "Initial psychiatric illness in involutional women" J. Ment. Sc. 103:132-145.

206. TEDESCHI, R.E., TEDESCHI, D.H., AMES, P.L., COOK, L., MATTES, P.A., and FELLOWS, E.J. (1959) "Some pharmacological observations on tranylcypromine (SKF trans 385); a potent inhibitor of monoamine oxidase" Proc. Soc. Exp. Biol. and Med. 102: 380-381.

207. TEMFIK, G.I. and WELLS, B.G. (1957) "The use of Arfonad for the alleviation of cardio-vascular stress following electro-convulsive therapy" J. Ment. Sc. 103:636-644.

208. THOMAS, D.L.C. (1954) "Prognosis of depression with electrical treatment" Brit. Med. J. 2:950-954.

209. THOMPE, F.T. (1959) "An evaluation of prefrontal leucotomy in the affective disorders of old age" J. Ment. Sc. 104:403-410.

210. TOOTH, G.C. and NEWTON, M.P. (1961) Leucotomy in England and Wales 1952-54. London: Her Majesty's Stationary Office.

211. ULETT, G.A. (1962) "Neurophysiological changes with electro-convulsive therapy". J. Neuropsychiat. 3:206-209.

212. VAISBERG, M. and SAUNDERS, J.C. (1961) "Amitriptyline in the treatment of depressive states" Dis. Nerv. Syst. 22:334-338.

213. VERNIER, V.G. (1961) "The pharmacology of antidepressant agents" Dis. Nerv. Syst. 22:1-7, supp.

214. VON ARNOLD, O.H. and FOTTL, G. (1961) "Die behandlung der endogenen depression mit amitriptyline" Wien. med. Wchnschr. 111:272-274.

215. WALTON, H.J. (1958) "Suicidal behaviour in depressive illness" J. Ment. Sc. 104:884-891.

216. WATTS, C.A.H. (1956) "The incidence and prognosis of endogenous depression" Brit. M. J. 1:1392-1397.

217. _____ (1960) "The problem of suicide in general practice" Proc. Roy. Soc. Med. 54:264-266.

218. WEISS, L.B. and PRESSMAN, M.D. (1961) "A comparison of imipramine (Tofranil) and amitriptyline (Elavil) in treatment of depression" Psychosomatics 2:293-296.

219. WEISSMAN, A. (1961) "Interaction effects of imipramine and d- amphetamine in non-discriminated avoidance" Pharmacologist (Washington, D.C.) 3:60.

220. WEST, E.D., and DALLY, P.J. (1959) "Effects of iproniazid in depressive syndromes" Brit. M. J. 1:1491-1494.

221. WILCOX, P.H. (1960) "Drugs and electroshock treatment" pp 535-539 in Progress in Neurology and Psychiatry. Volume XV (edited by E.A. Spiegel) New York: Grune and Stratton.

222. _____, and WILCOX, K.W. (1954) "Physiodynamic therapy (shock therapy)" pp 584-605 in Progress in Neurology and Psychiatry. Volume IX (edited by E.A. Spiegel) New York: Grune and Stratton.

223. WITTENBORN, J.R., PLANTE, M., BURGESS, F. and LIVERMORE, N. (1961) "The efficacy of electroconvulsive therapy, iproniasid and placebo in the treatment of young depressed women" J. Nerv. Ment. Dis. 133:316-332.

224. ZECK, P. (1961) Letter "The dangers of some antidepressant drugs" M. J. Australia, 2:607-8.

225. ZELGER, I. (1961) "La amitriptilina: una terapeutica eficaz en la practica dermatologica" Dia Medico 33:424-426.

226. ZIEGLER, L.H. (1939) "Depression as chief symptom" Psychiat. Quart. 13:689.